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Effects of Gold Compounds on Rat Behavior

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EFFECTS OF GOLD COMPOUNDS ON RAT BEHAVIOR

by

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Jonas Kaye

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ABSTRACT

Effects of Gold Compounds on Rat Behavior

by

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Seven rats were trained on Fixed Ratio 20 and two on Fixed Ratio 12 Escape Schedules until a stable baseline was established. Five of the subjects were administered gold thioglucose, three received gold thiomalate, and one was injected with gold, gold thioglucose, and gold thiomalate, allowing for an intrasubject comparison. Colloidal gold appeared to suppress response rate for one or two sessions, while gold thioglucose and gold thiomalate suppressed normal response rates from several to a number of sessions. This response rate suppression was often followed by gradual recovery, although in several subjects recovery of response rate could not be achieved prior to termination of the experiments.

The drop in response rate was more consistent for the gold thiomalate-treated subjects than for the gold thioglucose group. A toxic effect of the injected compounds was manifest as a loss of weight, which was regularly associated with a drop in response rate. This weight reduction was greatest in the gold thiomalate-injected animals, indicating that gold thiomalate is probably more toxic than gold thioglucose to rats.

Tolerance was developed for gold thioglucose and gold thiomalate, as indicated by smaller response rate decrements after repeated

injections of the compound. As a consequence of repeated drug administrations, the animals demonstrated that they could tolerate a 1 milligram per gram of body weight dose of gold thioglucose if the dosage was increased gradually from a low-dosage initial injection. This dosage of 1 milligram per gram of body weight is double the amount required to produce demonstrable hypothalamic lesions in the rat.[1] Previous investigations have failed to demonstrate this degree of tolerance in rats, primarily because the animals did not have the opportunity to adapt themselves to this treatment.

Decrease in spontaneous activity on a balance beam apparatus was observed in several rats following administration of the larger gold thioglucose dosages (i.e., 0.5 milligrams per gram of body weight to 1.0 milligram per gram of body weight), as well as following the administration of gold thiomalate.

Dosages of 20 milligrams to 50 milligrams of gold chloride were lethal to two rats.

The heavy dosage of gold thioglucose administered to the female rat subjects at Utah State University (i.e., up to 1 mg per gram of body weight), although potentially producing extensive hypothalamic lesions,[2] did not produce demonstrable hyperphagia or obesity, probably due to the anorexia and hypophagia associated with liver and kidney damage,[3] which could counteract the hyperphagia expected to be associated

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[1] J. W. Wagner and J. DeGroot, "Effect of Gold Thioglucose Injections on Survival, Organ Damage and Obesity in the Rat," *Soc. Exp. Biol. and Med.*, CXII (1963), 33-37.

[2] *Ibid.*

[3] W. D. Block, O. H. Buchanan, and R. H. Freyberg, "Metabolism, Toxicity, and Manner of Action of Gold Compounds used in the Treatment of Arthritis," *J. of Pharmac. and Exptl. Therap.*, LXXVI (1942), 355-357.

with the extensive hypothalamic lesions produced at dosages over 0.5 milligram per gram of body weight following gold thioglucose administration.[4]

(111 pages)

[4]Wagner and DeGroot, *op. cit.*

INTRODUCTION

Gold, gold thioglucose, and gold thiomalate are drugs which are currently utilized in medical practice in the diagnosis and treatment of cancer and rheumatoid arthritis (Drill, 1954). Yet, these compounds would not have received much attention from behavioral pharmacologists within the larger sphere of psychology, had not Brecher and Waxler (1949) discovered, following a single massive dose of gold thioglucose into a mouse, that within weeks the animals practically doubled its size from overeating (hyperphagia). The problem, which became obvious in time, was an apparent discrepancy between the obesity and hypothalamic lesions (Marshall, Barnett, and Mayer, 1955) produced following a gold thioglucose injection and a lack of obesity and overt symptoms in humans receiving this drug during arthritic therapy.

The purpose of this investigation was to evaluate the apparent effects that gold-containing compounds have on response rates and behaviors as related to chemical lesioning of hypothalamic areas and associated neural structures.

REVIEW OF THE LITERATURE

The complexity of gold and its compounds is of such magnitude--whether chemical, biological, or behavioral factors are considered--that it would be most advantageous to consider such phenomena separately, prior to attempting to integrate or combine these various attributes. A natural starting point is the history of gold and its derivatives.

Medical History of Gold and its Compounds

Gold, as one of the precious metals, was highly regarded as a medicinal agent in ancient times. It was said to be used in the treatment of syphilis at the time of Paracelsus (Drill, 1954). In the latter half of the nineteenth century, following the emergence of chemistry as a science, gold and some of its compounds regained their popularity as therapeutic agents based on a more rational basis. Gold compounds were widely used in the first half of the twentieth century to treat tuberculosis, rheumatoid arthritis, and skin diseases such as lupus erythrematosis.

Gold chloride was one of the earliest compounds of the metal gold which were utilized in medical practice. In Remington's *Practice of Pharmacy* (1905), an official compendium for the medical and pharmaceutical professions, gold chloride was combined with nitrohydrochloric acid to give gold and sodium chloride, the combination of which is medicinally equivalent to gold chloride. This salt mixture (i.e., gold

and sodium chloride) was used internally as an alterative at a dose of from 0.005 to 0.016 gm. By 1917, Holland had published his text, *Medical Chemistry and Toxicology* (Holland, 1940), in which he stated that the toxic effects of gold and sodium chloride are similar to those of mercuric chloride; i.e., gastro-enteritis, mental disturbances, and convulsions. Soon gold chloride disappeared from the scene as a medicinal agent. A closely-related drug, gold bromide, had come into prominence in the latter half of the nineteenth century, but it too fell into disfavor. In 1889, Goubert reported to the French Academy that gold bromide had a more efficacious and more durable action in epilepsy than the other bromides and that it was better tolerated (Wood, 1940).

Toward the middle of the twentieth century (Wood, 1940), medical opinion was that the soluble salts of gold are actively poisonous and that their toxic effects, like those of mercury salts, appear to be due to their local irritant action on the alimentary canal and on the kidneys. Perhaps it was due to the lack of reliable data about the gold compounds--or possibly other causes--that the medical profession continued utilizing the gold compounds in therapy, although on a smaller scale.

Currently, gold in its colloidal (i.e., finely divided metallic particles) radioactive form is a diagnostic agent for tumor detection (Drill, 1954), as well as in the treatment of the malignant tumors. Gold thioglucose and gold thiomalate are utilized frequently in certain cases of rheumatoid arthritis, and are considered to be the drugs of choice in such cases by some of the leading rheumalogists (Goodman and Gilman, 1965).

Colloidal radioactive gold can be given in small amounts intravenously (Root et al., 1954) in order to obtain scintiscan records over such organs as the liver. During the early stages of rheumatoid arthritis, gold thioglucose and gold thiomalate, as well as several other similar gold compounds, have been demonstrated to be associated with the reduction of the inflammatory process. The patient frequently reports relief from pain, but the mechanism of action remains unknown (Drill, 1954). A number of studies have been conducted to discover the mechanism of the action of gold compounds over the years, without demonstrable success.

Gold compounds (but not colloidal gold) are considered to be highly toxic by medical practitioners (Drill, 1954). Since the introduction of the gold compounds in arthritic therapy (i.e., chrysotherapy), the following manifestations of toxicity (Remington, 1965) have been frequently reported: pruritis, dermatitis, stomatis, gastritis, colitis; and rarely, blood dyscrasis, hepatitis, and neuritis. Although psychiatric abnormalities have only been infrequently reported (Hartfall, Garland, and Goldie, 1937), in an exhaustive review of the toxic effects of gold, Sundelin (1941) reported cases with central and peripheral nervous system manifestations. Cerebral symptoms ranged from simple depression to frank psychosis. In 1950, Myerson (1950) reported a case of meningitis as an unusual complication of chrysotherapy.

The Chemical Nature of Gold and its Compounds

Any consideration of the effects of a drug on a biological system necessitates an investigation of the chemical nature of the drug. One

of the reasons is that it has long been known that there is a definite relationship between the effects of drugs with similar chemical configurations or structural similarities and their actions on biological systems. Furthermore, the known solubility characteristics of drugs provide further clues as to possibilities of their distribution following administration. Finally, the chemical structure also allows an investigator to frequently predict the pharmacodynamic or metabolic changes which contribute to the final observed effects.

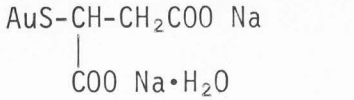
Metallic gold, the "noble" metal, was known and utilized both medicinally and ornamentally long before recorded history. It was one of the first metals to be utilized by mankind (Wood, 1940), and is found in many parts of the earth, occurring in both free and combined states. Its chemical symbol is Au. It is a yellow metal, with a specific gravity of 19.3 and atomic weight of 197.2, and when finely divided, it may show a red, purple, or black color. It has a valence of one or three when chemically combined. In its metallic form--which includes colloidal gold--the mineral is insoluble and highly unreactive.

Gold chloride, having the chemical formula $AuCl_3$ (Wood, 1940), is usually found in the form $AuCl_3 \cdot HCl \cdot 3H_2O$. It is a bright golden-yellow crystalline compound which is soluble in water. It is hygroscopic and contains approximately 50 per cent gold. By 1940, it was rarely prescribed because of its strong irritant action and is currently only of historical interest. The gold in the compound is trivalent and ionic (i.e., Au^{+++}). Gold chloride is unstable in water, so that on long standing it is changed (or reduced, in technical terminology) to its elemental state of zero valence; i.e., metallic

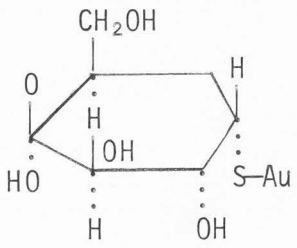
gold (Bjerrum, 1948). In an organic material such as sesame oil, this reaction occurs rapidly so that within hours the gold is in its metallic form (USU Laboratories, 1969). In biological fluids, rapidity of reduction of the trivalent ionic gold to its metallic form should proceed at an equal or greater rate than that observed with sesame oil.

Gold thioglucose and gold (sodium) thiomalate are technically members of the so-called organo-metallic compounds because they are composed of the metal gold attached to an organic moiety. What makes them interesting and complicated is that the gold in both compounds is held in what is called a coordination complex. This means that the gold is ionic in nature--at least to some extent--as in gold chloride, but is somehow protected from being reduced by the organic moiety to which it is attached. The practical significance of this coordination complex is demonstrated when the compound is put into sesame oil, for it remains stable for at least several months (USU Laboratories, 1969). Gold thioglucose has been long known (Merck Index, 1952a; 1968), and has been marketed under the trade name Solganol (manufactured by Schering). It is a yellow powder whose aqueous solutions are unstable on long standing. Gold thiomalate is marketed as Myochrisine (manufactured by Merck) and is a white powder. The fact that the drugs are currently available from the manufacturers suggests that they are still used therapeutically on humans suffering from rheumatoid arthritis.

The formulas for gold thioglucose and gold sodium thiomalate are as follows (Remington, 1965):



Gold sodium thiomalate



Gold thioglucose

Gold thioglucose is less soluble than gold sodium thiomalate. Gold sodium thiomalate, according to Drill (1954), is the only gold compound used medicinally which gives an appreciable concentration of ionic gold.

The Biological Distribution and Known Effects of Gold, Gold Chloride, Gold Thioglucose, and Gold Thiomalate in Animals and Man

Gold drugs were known and utilized medicinally for thousands of years prior to any precise scientific knowledge of their biological distribution and biological effects. Once the biological information was available--almost without exception, scientific gains were made in those areas. For example, digitalis was known for hundreds of years in England and was associated by all varieties of medical practitioners with the gout, but once it was found to specifically affect heart tissue and to be of a certain chemical structure, not only was it possible to utilize it in cardiology on a more rational basis, but the relationships which had been discovered between the type of drug and its biological target organ resulted in the discovery of a host of

other similar drugs, thus advancing the whole field of cardiology. This same argument applies to the gold compounds. Until their biological effects were discovered, no meaningful explanation could be made for their effects, for example, on operant behavior in rats. A functional relationship might have been observed (i.e., a drop or gain in response rate in relation to a drug injection); but without biological and chemical data, the causal relationship remains obscure. Consequently, it became imperative to review the data which has been accumulated to date on gold and its compounds.

Metallic gold in its colloidal form was found to be of great use in medical diagnosis and treatment of malignant tumors. It was considered for investigation in this study because of its continuing importance in medicine and its relation to the other drugs used in the following experiments. The colloidal gold and radioactive gold are normally administered in very small quantities (e.g., 5 mg). The advantage of the isotopic form of administration for our purpose is that it allows for charting of the distribution of the gold within the animal. In 1954, Root and his associates at the Oak Ridge Institute for Nuclear Studies (1954) studied the distribution and radiation effects of intravenously administered colloidal gold in a number of patients who had been injected with the radiogold. Their results, using a Geiger tube and radiograms, indicated that in man most of the gold (60 to 94 per cent) localized in the liver. The spleen was second in its ability to concentrate gold (5 to 16 per cent); while the kidneys and lungs and adrenals followed with decreasing concentrations. No gold could be found in the cerebral cortex. As for clinical effects, no immediate reactions were noted. Transient localized

tenderness of the liver was noted in the patient who received the largest dose of the isotope (Root et al., 1954).

Haigler and Williams (1951) injected radiogold in doses of 10.0 μc to 3 mc in albino rats by various routes, including the intraperitoneal injections. They reported that the gold was phagocytized by the reticulo-endothelial cells of the liver, spleen, lung, kidney, and bone marrow. Ninety to 95 per cent was taken out of the blood by the liver and spleen, with very small quantities going to reticular elements elsewhere.

Radioactive gold which was injected intraperitoneally into human patients (Beierwaltes, Johnson, and Lalari, 1957) mixed with the fluid of the cavity within the first few hours, after which from 50 to 90 per cent of the radiogold disappeared from the cavity. Part of the gold was shown to be attached to surrounding serosa, while a little of the gold entered the blood. The urinary excretion of gold was low, being greatest during the first day, but generally less than 0.04 per cent of the total dose per day. In Russia, Kalistratova, Moskalev, and Serebryakov (1966) injected colloidal gold (198 Au) into white rats. The routes of administration included intravenous, oral, endotracheal, and subcutaneous administrations. Their findings indicated that gold was slowly absorbed from the site of administration and accumulated mainly in the liver, spleen, and lymphatics. Gold administered parenterally was excreted slowly in the first four days.

Radiogold has also been injected directly into glands (e.g., intramammary injection) (Berg and Christophersen, 1956). In these cases, it was not distributed for any appreciable extent throughout the body. In Berg and Christophersen's study, in which 60 dogs were injected in

the mammary glands with the isotope gold, the radionuclide concentrated in the axillary, cervical, and latissimus dorsi lymph nodes--structures closely adjacent to the injection site.

Such studies of the distribution of colloidal gold indicate that the final target organ for the deposition of gold is associated with the route of administration, so that if several animals are to be compared, identical routes of drug administration are required.

Gold chloride is now known to be too toxic as far as injections into humans is of concern. But over the years, investigators have been interested in the biological effects of gold chloride in animals. Elftman, Elftman, and Zwemer (1946) carefully studied the histochemical distribution of gold following the intraperitoneal administration of gold chloride into rats and guinea pigs. A most interesting observation which they made was that the gold (chloride) was not reduced to the metallic state at the time of deposition in tissues; but, rather, he found in those tissues refractile granules of gold whose chemical nature remained undetermined, but may be related to the gold-protein complexes. The concentration of gold chloride deposition in animal organs decreased in the following order: epitheluim of the proximal convoluted tubules of the kidney; phagocytic cells, including the histocytes of connective tissue in general and the capsules of organs; the Kupffer cells; and the reticular cells of the lymph nodes.

The total amount of gold chloride received by each animal ranged from 0.034 mg to 0.43 mg per gram of body weight.

The biological effects of gold chloride were also reported by Orestano (1932). Orestano's findings were that when gold chloride is given hypodermically, it is partially absorbed, producing death with

large doses; the rest of the gold chloride (i.e., the unabsorbed) is changed to metallic gold. Rapid intravenous injections resulted in a minimal lethal dose of 0.0008 g/kg of body weight. Orestano reported that the pharmacological action was due to the gold ion, which produced intense hemolysis and hemoglobinuria. The mineral was fixed in the red corpuscles more than in other parts of the body. Orestano described the following transformation for gold chloride: complex gold ion → gold cation → metallic gold.

As gold thioglucose and gold thiomalate are soluble gold compounds, as is also gold chloride, after injections of these compounds, metallic gold was deposited in largest quantities in the kidneys, which was in striking contrast with the large amount of gold that localized in the liver following injections of colloidal gold compounds (Block, Buchanan, and Freyberg, 1942). Gold was also located in the heart, lungs, and spleen, as well as at the injection site, following administration of gold thioglucose and gold thiomalate.

So far, we have been dealing with systemic abdominal distributions, which are the limiting distributions for colloidal gold and gold chloride as indicated by the available data. In addition to the abdominal distributions of gold following the administration of gold thioglucose and gold thiomalate, it was demonstrated by Mayer (1960) and Wagner and DeGroot (1963) and subsequent investigators that the brain itself is invaded by these compounds. Gold deposition in brain tissue is of great interest to psychologists because of the possibility of associated behavioral effects.

Gold thioglucose and gold thiomalate, which contain the metal in chelate linkage (Beckman, 1958), although not the only metals which

can penetrate the brain, are of particular interest to psychologists because studies have linked them with abnormal hypothalamic functioning and some nutritional problems (Mayer, 1960). The first study (Marshall, Barnett, and Mayer, 1955) demonstrated that gold deposited in the ventro-medial nucleus (VMN) of the hypothalamus after a single large injection of gold thioglucose into mice. In addition to the VMN lesions demonstrated by Marshall, Barnett, and Mayer (1955), Liebelt and Perry (1957) demonstrated that significant lesions were also induced in the lymbic system of mice (i.e., fornix, ventral psalternus, and primordial hippocampus), as well as in the hypothalamus. By 1960, Swartz, Christian, and Andrews (1960), using radioactively-tagged elements (i.e., Au 198 and S32), observed the sites which gold and thioglucose each occupied at various intervals up to 48 hours following the gold thioglucose injections. They found labeled gold in the mouse's cerebrum, hypothalamus, and hindbrain. Mayer's (1960) work at that period indicated that hypothalamic lesions were produced in rats by the administration of gold thioglucose, as well as in mice, but the rats did not survive the massive doses because of toxic effects. Thus, Mayer concluded that while the lesions can be induced by gold thioglucose in rats, obesity cannot, since it requires the survival of the animal. In 1962, Debons et al. (1962), utilizing histological and autoradiographic techniques, demonstrated that there was a predominant accumulation of gold in the middle section of the brain, which included the hypothalamus. The radioautographs indicated that although gold thiomalate penetrated brain tissue and was deposited as gold, the disposition was diffuse in comparison with gold thioglucose, in which the heaviest concentration was within the VMN of the hypothalamus. The animals which

received gold thioglucose, but did not develop hypothalamic obesity, characterized by hyperphagia and subsequent obesity, had the lowest content of gold in the midsegment (which included the hypothalamus). Debons et al. (1962) also injected 75 mice with gold thiomalate. Although none of the 75 mice became obese, there was a significant amount of gold noted in the brains of the gold thiomalate-treated mice. The distribution of gold in the brain of the gold thioglucose-treated non-obese animal was too diffuse to be localized in discrete areas even after prolonged exposure of radioautographs. It was also noted in this study that there was no radioautographic evidence of gold accumulation in the hypothalamus of the animals which were treated with gold thioglucose but did not become obese; nor did any of the gold thiomalate-treated animals show radioautographic gold localization in the hypothalamus, although gold was distributed diffusely throughout the brain in every case.

Mayer (1960), after injecting several hundred mice with varying dosages of organo-metallic gold compounds, was able to establish statistics for lethal dosages.

Gold thioglucose was demonstrated to be the only gold compound to produce obesity in the mouse, and the lethal dose (i.e., LD 50) was determined to be approximately 1.0 mg per gram of body weight--a dosage which produced obesity in approximately 50 per cent of mice following injection.

Although the hypothalamic area involved is often very large, only hyperphagia appears to result (Marshall, Barnett, and Mayer, 1955), and it appears that the presence of the glucose component in the gold thioglucose molecule makes this restricted hypothalamic portion of the

blood-brain barrier much more permeable to this compound than to compounds not containing glucose. The hypothalamic area containing the feeding centers had been previously postulated to contain "gluco-receptors" (Mayer, 1953). The lesions formed were permanent in animals which in fact became obese, but were not apparent in animals unsuccessfully injected. Gold thiomalate, though as toxic as gold thioglucose (Mayer and Marshall, 1956), did not cause obesity or hypothalamic lesions. Mayer and Marshall (1956) also tested sodium thioglucose along with the gold thiomalate. Sodium thioglucose and gold thiomalate injections of varying dosages did not produce obesity, while gold thioglucose (Marshall, Barnett, and Mayer, 1955) was responsible for observed obesity. Mayer and Marshall (1956) had shown that rats appear to be more susceptible to the toxicity of gold compounds in general.

Brain damage, as a cause of gastric ulceration in animals, was first demonstrated by Schiff in 1846, and later confirmed by many investigators. More recent work indicates that the hypothalamus plays a prominent role in the formation of such lesions. Consequently, Deter and Liebelt (1962) injected rats intraperitoneally and intramuscularly in dosages of 0.2 mg to 0.5 mg per gram of body weight and reported that a single injection of gold thioglucose produced gastric ulcers and hypothalamic lesions in 100 per cent of injected rats if proper experimental conditions were chosen. Doses of gold thiomalate and gold chloride, which killed animals within 24 hours (Deter and Liebelt, 1962), produced neither hypothalamic nor gastric lesions; although in the case of gold chloride, animals injected with only 0.04 mg per gram of body weight of the compound killed three out of the 10 rats within 24 hours following injection.

Gunter and Ivy (1949) tested Hench's (1940) hypothesis that the ameliorating effect of gold in rheumatoid arthritis is perhaps analogous to, if not basically identical with that induced by intercurrent jaundice. Gunter and Ivy used two dogs which were in good health, weighing 13.2 and 14.1 kg, as their subjects. They injected gold thioglucose and gold sodium thiomalate to both dogs for a period of three weeks. A total of 1500 mg of the combined drugs were administered to each dog (i.e., 800 mg of gold sodium thiomalate and 700 mg of gold thioglucose). They followed the gold administrations with laboratory tests for liver function and their data indicated that in no case did any of the liver function tests show a variation beyond the normally accepted values. Their results did not support Hench's hypothesis that a case of jaundice following gold injections should relieve a patient's suffering. No behavioral changes were reported by Gunter and Ivy (1949), although it should be noted that in terms of the dog's body weight (i.e., 14 kgms), and knowing that gold thioglucose has an LD50 of 1 mg per gm of body weight for mice (Mayer, 1960), a divided dosage of 1500 mg represented approximately 10 per cent of the comparable lethal dose. Still, this amount was not sufficient to produce extensive hypothalamic effects in the animals.

In rats, administration of sublethal dosages of gold thioglucose (i.e., 0.4 mg per gram of body weight (Wagner and DeGroot, 1963)) produced bilateral lesions in the ventromedial aspect of the hypothalamus in 90 per cent of the rats, although obesity did not result at this dosage level.

Chang and Persellin (1968) injected gold thiomalate into guinea pigs (2.1 mg gold sodium thiomalate per week) and reported that the

experimental subjects gained significantly more weight than the controls. They detected gold in the hypothalamic and thalamic sections of treated animals when they used the technique of neutron-activation analysis. Brain sections from control animals did not contain gold. Chang and Persellin's study (1968) extended the species generality of the brain effects of administration of gold compounds.

Cortell and Richards (1942), using rat subjects, demonstrated the development of tolerance to gold salts in rats, using the survival method. They showed that rats given sublethal dosages of gold sodium thiosulfate and of gold sodium thiomalate could tolerate ordinarily lethal dosages of these compounds when subsequently administered. Denko and Anderson (1944) also used a similar technique to test the toxicity of gold compounds and noted that sublethal dosages of gold thioglucose showed a decided rise in blood nonprotein nitrogen values (a technique for quantifying one form of toxicity) which returned to normal the fifteenth day. When the dosages of gold thioglucose were repeated on these animals, blood nonprotein nitrogen values remained normal. A third dose of 75 mg also showed no appreciable rise in the blood nonprotein nitrogen value. Gold compounds were also frequently switched in this procedure, thus enabling Denko and Anderson (1944) to demonstrate both a direct tolerance and cross tolerance for the gold compounds.

There are also a number of related metabolic factors affecting the deposition (and perhaps the transport) of gold thioglucose. For example, Edelman et al. (1965) have gathered data which indicate that glucose concentrations in the blood of the animal subject that prevailed at the time of the gold thioglucose injection was directly

correlated with the hypothalamic uptake of gold, with the extent of the hypothalamic lesion that resulted, and with the severity of the subsequent hyperphagia and obesity. They found that hyperglycemia or high blood sugar was associated with an increased gold deposition throughout the brain.

Likuski, Debons, and Cloutier (1967) found that the glucose inhibitors, 2 deoxy-D-glucose and 2-amino-2 deoxy-D-glucose, both markedly inhibited gold thioglucose-induced hypothalamic obesity. Likuski, Debons, and Cloutier (1967) confirmed the hypothesis that a glucose inhibitor (such as 2 deoxy-D-glucose) interacts with cells in the postulated satiety center. Such metabolic inhibitors could significantly affect the outcome of the gold thioglucose injection if they should occur in appreciable quantities in the animal's vascular system at the critical time. As for the environmental variables, Likuski, Debons, and Cloutier (1967) noted that the room temperature at the time of the gold thioglucose injection plays an important role in the incidence of obesity, obtaining a 100 per cent incidence of obesity by maintaining a constant room temperature of 21 C ± 2 C at the time of the gold thioglucose administration.

Behavioral Effects of the Gold Compounds

Behavioral effects of drugs may be considered to be either desirable or toxic. Any undesirable behavioral characteristic may be defined arbitrarily as behavioral toxicity if it should follow the administration of a particular drug. Such a definition would be most arbitrary. The question arises whether a more rational approach to the subject may be taken. The answer suggested is that the term "behavioral

toxicity" could be a general term for behavior resulting from a specific drug administration in which the consequent behavior is in some manner non-adaptive for a particular member of a species. Appropriate examples would be such effects as loss of thermoregulatory control for a species whose home is in a cold environment, or muscular spasms in an animal which normally has to maintain itself at treetop level. In such a context, behavioral toxicity becomes meaningful and, furthermore, clarifies what might be considered appropriate behavioral effects for a particular animal in a given environment.

The behavioral effect which brought the gold compounds into prominence for psychologists and nutritionists was the result of an accidental finding made by Brecher and Waxler (1949) 20 years ago.

A number of behavioral effects had been noted to be associated with hypothalamic lesions prior to 1949; i.e., hyperexcitability (Hetherington and Ranson, 1942); abnormality of the reproductive organs, and of mating behavior (Bard, 1940; Dey, 1943). Waxler and Brecher (1949) injected mice with the organo-metallic chemical gold thioglucose in order to study the drug's toxicity. They noted that within days, the animal's size markedly increased. As a result, they decided to carefully investigate the phenomenon. Brecher and Waxler administered a single intraperitoneal injection of 25 mg to 35 mg of gold thioglucose to albino mice, with resulting marked weight gains in about 10 to 14 weeks. A post-mortem analysis was conducted for total body lipids, proteins, water, and ash. They concluded that the gain in weight in the mice was primarily due to an increase in adipose tissue. Brecher and Waxler (1949) described the characteristics of their gold compound. They stated that it was made up of 50 per cent

gold, was unstable in water, and was hygroscopic. To maintain the compound in a stable form, they used sesame oil as the vehicle. Although gold thioglucose is fairly stable in aqueous solutions (Remington, 1965), gold thioglucose in sesame oil allowed for even greater stability. Brecher and Waxler (1949) determined that the lethal dose, arbitrarily defined as the dose at which 50 per cent of the animals die, was 40 to 50 mg intraperitoneally for mice weighing 20 to 25 gms. Fifty to 70 per cent of their animals survived doses of 35 mg of gold thioglucose, and 90 per cent survived dosages of 25 mg. All animals survived doses of 12 mg injected intraperitoneally. Fatalities from the administration of gold thioglucose generally occurred during the first three to four days. There was no further mortality among those animals which survived one week. Only about one-third to one-half of the gold thioglucose-injected animals showed unusual weight gains. Animals that failed to show significant weight gains by the eighth week were given another 25 or 35-mg dose of gold thioglucose. Significant weight gains were subsequently observed in a number of reinjected animals. Animals, when given injections of only 5 mg of gold thioglucose intraperitoneally twice a week until a total of 150 mg were given, failed to show any significant weight gains. All animals used in the above experiments were killed at the end of 14 weeks. The viscera and the brains of both injected and control animals were examined microscopically. Except for centrolobular infiltration of the liver in obese animals, no anatomical lesions were formed in the organs examined.

The significance of hyperphagia (overeating) and subsequent obesity following the administration of gold thioglucose in mice subjects has

stimulated research efforts by behavioral investigators and medical researchers concerned with nutrition.

Following the investigations of Brecher and Waxler (1949), possibly the earliest use of operant procedures to study hypothalamic obesity was that of Miller, Bailey, and Stevenson (1950). By this date, it was known that gold thioglucose injections were followed by obesity in the mouse (Brecher and Waxler, 1949), but hypothalamic lesions had not been associated with the obtained data.

Miller, Bailey, and Stevenson (1950) stereotaxically induced hypothalamic lesions in their subjects and sought to answer the question of whether the marked increase in food intake produced by the lesion in the hypothalamic subject would be accompanied by increased performance in a variety of behavioral tasks motivated by hunger. The following procedures were used: (1) rate of bar pressing, reinforced by food at five-minute intervals; (2) amount of electric shock required to prevent approach to food; i.e., negative reinforcement in an approach-avoidance situation; and (3) amount of food eaten in spite of a bitter taste (produced by mixing quinine with the food). Miller, Bailey, and Stevenson (1950) concluded that in ad libitum feeding situations, animals ate increased quantities of food following lesions, but generally did not work for the same quantities of food; i.e., the "drive" to obtain food--as indicated by performance--was weak in comparison with expectations from the consummatory behavior noted in ad libitum feeding situations.

The likelihood of a specific causal or functional relationship between a brain lesion and subsequent obesity in an animal subject, with an accompanying explicit statement of the mechanisms involved,

was explored in 1955. In that year, Bates, Zomzely, and Mayer (1955) noted that the instrumental behavior of overeating (hyperphagia) in obesity was not necessarily simple, as the hyperphagia may be the secondary result of an abnormal fat metabolism--either increased rate of synthesis, decreased fat mobilization and oxidation, or an imbalance between the two, with a net gain in favor of synthesis. It could also, they hypothesized, be due to an entirely different cause.

A most enlightening study by Anliker and Mayer (1956) utilized operant procedures to measure feeding behavior patterns in demonstrating a change from normal feeding to increased intake at each meal with gold thioglucose-injected mice. Mayer (1953), who had written on the genetic, traumatic, and environmental factors in the etiology of obesity, and Anliker (Anliker and Mayer, 1956), undertook this investigation. Their subjects were mice with three types of obesity produced by different methods; i.e., hypothalamic obesity, produced by stereotaxically lesioning the ventromedial nuclei of the hypothalamus; gold thioglucose obesity, resulting from a single injection treatment with gold thioglucose; and hereditary obese hyperglycemia syndrome, a Mendelian recessive characteristic that originated from crossing of "V stock" males and "C57 BL16" females. The cumulative records of Anliker and Mayer's study represented prolonged studies of several animals of each type and illustrate the food intake patterns. Anliker and Mayer (1956) were able to demonstrate that the over-all rate of feeding was greater for the hyperphagic mice--including gold thioglucose-obese mice--than for the normal controls; and that waves or cyclic changes in rates of feeding were characteristic of normal mice, but were absent or barely discernible in the hyperphagic mice. They

concluded that gold thioglucose-obese animals and hereditary-obese animals are the same, or approximately so. This conclusion was different from the one reached by Bates, Zomzely, and Mayer (1955), when they noted that large differences existed between hereditary-obese mice and their siblings made obese by a single injection of gold thioglucose in relation to food intake and spontaneous exercise.

Schmaltz and Issacson (1968) stereotaxically produced caudate lesions in rat subjects to test for retention and relearning of an operant reinforcement schedule. Transient, post-operative impairment was noted, and recovery on the schedule was generally noted by the tenth post-operative day. It was noted that impairment could be noted from the transient behavioral decrements; but the brain-damaged subjects recovered, although recovery required at least a week or two for reestablishing the baseline. Such results have possible implications for drugs damaging brain tissue.

In 1960, Mayer reported that the hypothalamic lesions induced by gold thioglucose in mice are much more "purely" hyperphagic than lesions induced in the same area by electrolytic coagulation. Although gold thioglucose lesions were widespread, they appeared to be selective. Mayer (1960) also reported that it is well known that there are all sorts of disturbances in functions other than food intake in animals in which lesions have been induced electrolytically with a stereotaxic instrument; but by contrast, animals made obese with gold thioglucose seem to be only hyperphagic. They breed, have normal litters, and nurse their young.

Mayer's report (1960) of normal breeding in mice following gold thioglucose administration was not supported subsequently, for in 1966

Rudali and Silberman (1966) injected female AkR mice intraperitoneally with gold thioglucose and subsequently observed that they were sterile. With male mice, they reported sterility in spite of normal spermatogenesis.

Although hyperphagia was the most frequently reported behavioral effect in mice since Brecher and Waxler's investigations of 1949, other behavioral effects of a toxic nature were reported by Wagner and DeGroot (1963). Following the injection of 63 male Long-Evans rats with varying dosages of gold thioglucose (Wagner and DeGroot, 1963), varying from 0.1 to 0.75 mg per gram of body weight, within 12 hours after injection all rats exhibited aphagia, adipsia, enuria, evidence of lowered body temperature (i.e., shivering), increased sensitivity to a variety of stimuli, mild tremors, and the onset of convulsions, which invariably preceded death in rats given lethal dosages of gold thioglucose. Such symptoms are additional manifestations of behavioral toxicity attributed to gold thioglucose administration.

In the case of gold thiomalate, reactions have been attributed to the compound during arthritic therapy. Strauss, Barrett, and Rosenberg (1950) report that toxic reactions to gold in humans resulted from small amounts in some cases and large amounts in others. In one patient, only 20 mg of gold were sufficient to induce a serious reaction; in another, toxicity did not appear until 7900 mg had been administered. In 86 per cent of the cases, the toxic reaction to gold consisted of pruritis, dermatitis, or stomatitis. Occasional bone marrow depression, hepatitis, or nephritis was reported.

In the case of gold, as had been suggested (Root et al., 1954), the administration of Au^{198} intraveneously causes little untoward effects

in the patient. In a few cases (Root et al., 1954) there was anorexia for a few days; and in one patient, transient liver tenderness. Liver function tests showed no significant changes following the gold administration.

Gold chloride is now known to be quite toxic, so that the most predictable effect following appreciable dosage administration would be the death of the subject.

Behavioral toxicity has already been previously attributed to gold thioglucose administration to humans; i.e., psychiatric disorders, central and peripheral nervous system manifestations (Sundelin, 1941), and polyneuritis leading to flaccid paralysis of all limbs (Leiper, 1946). Such disorders, not conducive for adaptation to the environment, fall under the behavioral toxicity classification.

Although most toxic effects of gold compounds in the case of human subjects are expressed as verbal expression or operant behavior, an interesting exception (i.e., electro-physiological evidence) was reported by Patterson and Dale (1966). They reported that more abnormal EEG frequencies, particularly fast wave findings, appeared in rheumatoid arthritis patients who had received large amounts of gold over a period of many years.

It became evident from data obtained from many sources that the neuroanatomical, neurophysiological, and behavioral changes following administration of gold compounds were much more complex than they were previously believed to be. From Mayer's (1960) work, it was indicated that gold thioglucose lesions are associated with hyperphagia and obesity in mice, but not with gonadal dysfunction. Liebelt and Perry's (1957) data indicate that significant lesions were induced in the

limbic system, as well as in the hypothalamus, thus directing future research into the area of limbic damaged tissue, and possibly associated emotional changes. Swartz, Christian, and Andrew's (1960) administration of gold thioglucose into mice indicated a widespread deposition of gold into brain areas, with the probability of modifying behavior and relieving pain through the alteration of pain pathways. Debons et al's. (1962) data demonstrated differential deposition of gold in brain regions following the administration of gold thioglucose or gold thiomalate and the differential gold deposition in the hypothalamic areas following the injection of gold thioglucose and gold thiomalate. Brecher et al. (1965) obtained experimental data which indicated that the ventro-medial nucleus of the hypothalamus did not have to be the damaged tissue associated with the subsequent obesity; but rather, that the glucoreceptive sites may be widespread as to anatomical site. Likuski, Debons, and Cloutier (1967) showed that glucose inhibitors can interact with the hypothesized anatomical deposition sites, thus preventing the fixation of gold to hypothalamic tissue. Reynold's (1965) data and his proposed irritative theory, although in agreement with the experimental findings of widespread gold deposition, allowed for the irritation of the lateral hypothalamus, but contradicted the theoretical foundations of the old explanatory hypothesis for the mechanisms controlling food intake. This contradiction created a need for new experimental approaches and effort. Finally, Hoffman and Whistler's (1968) data on the effects of thioglucose--which were assumed to be non-contributory--turned out to be quite metabolically significant, causing a temporary glucosuria and hyperglycemia, and thus complicated the interpretations of the effects

which followed the administration of gold thioglucose into animals and humans.

Cox, Kakolewski, and Valenstein's (1969) most recent study of ventro-medial hypothalamic lesions and changes in body weight and food consumption in rats was closely allied to that undertaken at Utah State University. Subjects were both male and female rats, four months of age. After two weeks of baseline measurements, Cox, Kakolewski, and Valenstein's experimental animals received bilateral lesions of the ventro-medial hypothalamus, utilizing a stereotaxic instrument. Controls were subjected to the same treatment as the experimental subjects--including free feed--except that stereotaxic lesioning was omitted in the case of the controls. Female controls did not vary significantly in weight during the three weeks following surgery from their initial weight (i.e., 275 gms). In the case of the ventro-medial hypothalamic damaged subjects, weight averages increased from an initial weight of approximately 275 gms to a final weight of slightly over 350 gms--indicating hyperphagic behavior. Lesioning of the ventro-medial hypothalamus (Cox, Kakolewski, and Valenstein, 1969), then, led to substantial demonstrable weight gain in female rats within a three-week period following stereotaxic lesioning of the ventro-medial hypothalamus.

The Characteristics of the Measurement Technique

An essential consideration with operant procedures, particularly an escape schedule (since the escape schedule was utilized in these studies), was the ratio length effect noted in Dinsmoor and Winogard's

(1958) study. The responding rate of subjects on shock schedules was analyzed after first stabilizing the animals for several sessions at a given level of current and then taking a new series of readings at higher or lower shock levels. Their data indicated that as shock was increased, response rate increased, and visa-versa. Although the rate of response generally increased with increase in shock intensity--assuming that the subject did not stop responding altogether--there was an important length of ratio effect which was of particular significance with drug studies. Winogard (1965) studied escape behavior under different fixed ratios and shock intensities. His data indicated that for a subject on a long fixed ratio (e.g., FR20), the rate is lower than for a short fixed ratio (e.g., FR5). The difference in rate for different length schedules (Winogard, 1965) might be attributed to breaks occurring after the ratio run was under way. These breaks or pauses have been called "strain" by such investigators as Boren and Ferster and Skinner (Winogard, 1965). From such data it can be assumed that on long ratios (e.g., FR20), if rates of response by the subject are very high, the strain will be eliminated and drug effects should be less than, for example, the same FR (ratio) in which the subject responded at a lower rate and, consequently, strain was notable. With a short fixed ratio there was generally no strain and the rate of responding was at a higher rate (Winogard, 1965) so that less disruption by drugs was to be expected. It is evident from Winogard's data that rate changes following drug administration on a long ratio might not be comparable to those for a short ratio, so that the investigator might benefit by using at least one additional ratio length, either much longer or shorter than the main ratio for the experimental schedule.

The dose-curve relationship (Thompson and Schuster, 1968) is a very useful conventional pharmacological technique for measuring behavioral changes in the experimental session following the injection of a drug. It is often assumed, consequently, that the behavioral changes noted on the curve during the session are due to, or associated with, the drug action.

In the case of drugs such as the gold compounds, however, the concept has to be stretched to include post-experimental drug sessions. Under such conditions, samples of behavior demonstrated in the curves before drug injection must be compared with sample sessions after the injection. In this connection, for example, Barnes and Stoner (1959) studied the action of triethyl tin. Rats were given a single dose at about the LD50 for that drug, producing a transient narcotic action, after which the animal at first recovers (Barnes and Stoner, 1959), and then over the next two to three days it becomes quieter and progressively weaker and dies. Obviously, should such rats be subjected to operant procedures the first session, or even the first several sessions--although producing a definite drug dose-curve effect--taken individually it provides insufficient data for interpretations, and would be quite misleading if the before and after records were not studied session by session to note in what sessions the drug had its maximum or minimum effects, even though only one injection had been administered.

Barnes states the problem when he notes that

> many drugs that affect behavior can have the most rapid and dramatic effects which are nevertheless completely and often equally rapidly reversible. A number of centrally acting poisons, on the other hand, act much

> more slowly but in many cases irreversibly. (Barnes, 1964, p. 172)

The latter statement possibly applies to gold compounds.

Summary and Interpretations of the Gold Compounds Literature

The chemical characteristics of drugs, as well as their distribution in the organism and their biological, as well as behavioral effects, when considered in relation to each other--as mentioned earlier--allow for a rational interpretation of effects, as well as providing a framework for inferences and predictions.

Gold thioglucose and gold thiomalate, existing as chelates, in some not-too-well-understood fashion maintain the ionic or partly ionic state of the gold part of the molecule, and thus provide a possibility for a slow but reactive gold interaction with biological materials prior to some sort of deposition in the tissues. The compounds are both soluble, and since reactions are protected, the drugs may travel extensively throughout the body of an animal or man prior to reacting with tissue. Wagner and DeGroot's (1963) data, in which animals were sacrificed within 48 hours after treatment, provided histological evidence for hypothalamic lesions, clearly showing that the drug must distribute itself widely within that time. This would include passing the blood-brain barrier, in order for the compound to reach its deposition site within the hypothalamus. Swartz, Christian, and Andrew's (1960) data indicated that gold thioglucose could be picked up in high concentrations in the brain within two hours.

Gold chloride, being a trivalent gold compound, is the most reactive, but it has not been localized in brain tissue. As Orestano

(1932) claimed, it was highly reactive, damaging tissues rapidly and widely as it became distributed, with renal damage that led to fatality. Gold chloride, then, might be considered the most toxic of these gold drugs, although the toxicity must be restricted to abdominal areas at the current state of our knowledge.

Hoffman and Whistler's (1968) finding that the thioglucose part of gold thioglucose increases the glucose levels of the blood temporarily and Deter and Liebelt's (1962) finding of gastric lesions associated with the hypothalamic lesions both contribute markedly to the anorexia which is reported when higher dosage levels are administered (Wagner and DeGroot, 1963).

In the case of gold thiomalate, in spite of the similarity of the drug in structure to gold thioglucose it is known to diffuse in all areas of the brain (Debons et al., 1962), rather than concentrating in the VMN of the hypothalamus (as with gold thioglucose); and from a chemical point of view, it is more soluble and more ionic than gold thioglucose. Such a chemical difference can lead to greater reactivity and toxicity for gold thiomalate in comparison with gold thioglucose.

Behaviorally, colloidal gold would seem to fall into the relatively inert status, gold chloride toxicity should lead to deterioration of behavior and finally death; while gold thioglucose and gold thiomalate administration should fall in between. For example, the drugs in human administration have been followed by clinical reports in which the arthritic condition is improved (Drill, 1954) in a percentage of the cases, particularly where toxicity occurs. The patient frequently reports that the subjective experience of pain associated with the joint disease is reduced. Gold thiomalate has also been

used routinely for years in animal arthritis with reports of observed improvement in the locomotion of the animal (Fennel, 1969), thus demonstrating behavioral modification effects.

The most obvious difference between gold thiomalate and gold thioglucose and the other two gold compounds (i.e., gold and gold chloride) is that the two organic-metallic compounds deposit in both the body and brain of most species studied so far; but in the case of gold and gold chloride, whatever are its systemic effects, the drugs reportedly do not penetrate the brain.

An important consideration in relation to all gold compounds deals with what the pharmacologists call pharmacodynamics. Typically, drugs (e.g., phenobarbital) are soluble in biological tissue, are distributed rather evenly except for the target organ (where the concentration is assumed to be greater), and do their work (i.e., pharmocodynamics) by temporarily depressing or stimulating a particular tissue or organ, and are subsequently eliminated. In the case of the gold compounds, the most obvious implications for a pharmacodynamic explanation must include the fact that gold compounds are quite different from most classifications of drugs in that the final end-product of a gold injection includes the deposition of metallic gold within tissue. Not only can function be altered by such tissue alterations, but the probability of differential deposition of the gold on a particular occasion following drug administration could conceivably produce variability in effect in the same manner that neuro-surgical operations produce unpredictable after-effects on patients. This characteristic of gold would tend to produce variability in demonstrable functional relationships for the drugs. Furthermore, the evidence for tolerance

of gold compounds (Cortell and Richards, 1942; Denko and Anderson, 1944), using a non-protein nitrogen index, would be expected to be reflected behaviorally in a more constant response rate over sessions following the development of tolerance to the toxic drugs.

STATEMENT OF THE PROBLEM

A major problem of interest in relation to gold compounds and their effects on different species is the apparent discrepancy between the brain lesion and obesity produced in mice following administration of a large gold thioglucose dose and the apparent absence of similar phenomena in rats and other species, including man. The therapeutic gold thioglucose injections of patients suffering from rheumatoid arthritis have not been associated to date with brain lesions or obesity.

Hypotheses stated in relation to the basic research design and data collection techniques include the following:

1. Gold thioglucose and gold thiomalate effects following injection are different from those obtained either from gold or gold chloride.

2. Gold thioglucose and gold thiomalate should decrease response rates due to the neurological damage they induce.

3. Gold chloride, because of its reactivity, should be highly toxic to rats.

4. Colloidal gold, because of its inertness, should produce no behavioral effects.

5. Gold thioglucose-lesioned (or assumed to be lesioned) subjects should not react in the expected fashion under conditions in which anaphylactic shock would be expected.

6. Some differences in behavior might be expected following administration of gold thioglucose and gold thiomalate because of their chemical differences and different brain deposition.

7. Paralleling the data indicative of biological tolerance for gold compounds (Denko and Anderson, 1944), behavioral tolerance or adaptation following repeated administration of either gold thioglucose or gold thiomalate should be demonstrable.

8. Hyperphagia and weight gain in rat subjects could follow administration of heavy dosages of gold thioglucose.

EXPERIMENT I

Since colloidal gold strongly contrasts with gold thioglucose and gold thiomalate in reportedly being chemically inert, it was used as a gold control. Sesame oil served as a vehicle control. Based on this chemical difference, it was expected that gold would affect the animal in the same manner behaviorally as other gold compounds, but to a lesser extent. Gold chloride was reduced to elemental gold in sesame oil. It was assumed that the gold was primarily of colloidal size after reduction.

Method

Subject

A single Long-Evans female rat (R12), three months of age, served as the subject. The rat had not been previously used as an experimental subject.

Apparatus

The apparatus consisted of a relay-timer switching apparatus and an operant conditioning chamber equipped with a lever, stimulus lights, and a scrambling grid for shock delivery. The relay-timer switching apparatus is programmed for controlling behavioral contingencies. In addition, a cumulative recorder allowed for event recordings, such as lever-pressing responses.

Automatic recording of the number of responses emitted by S is programmed, as well as number of reinforcements, time out (or relief

from shock) delivered, inter-response times (IRT's), and the number of time-out responses; i.e., responses following shock termination.

Procedure

In the Escape Schedule utilized in this experiment, the operant behavior or response is reinforced by the termination of an unconditioned negative reinforcer, such as electric shock (Thompson and Schuster, 1968). The negative reinforcer or shock (i.e., S-) controls the occurrence of the responses.

The establishment of a baseline, incorporating the response rates data of a number of sessions prior to administrating a drug, allowed for utilization of the procedure in which each subject could serve as its own control, with baseline data serving as the criterion for interpretation of response rate variations associated with drug injections, as well as variations during the post-drug injection sessions. (See Cox, Kakolewski, and Valenstein, 1969.)

At each experimental session, the subject (R12) was lifted out of its home cage, weighed, carried into the experimental room, and placed in the operant chamber (after being observed on the balanced beam apparatus). The experimenter (E) left the room after turning on the apparatus. This initiated a 50-minute experimental session utilizing an Escape Schedule.

The initial experimental sessions consisted of training the rat to respond to terminate shock. This was accomplished by initially terminating shock after each bar press (i.e., FR1 or CRF), followed by increasing the number of bar presses which had to be emitted in order to terminate the shock for 30 seconds. The subject was trained

to a terminal level of a fixed ratio of 20 responses (i.e., FR20), followed by a 30-second relief or time out from shock. Following termination of a session, the animal (R12) was returned to its cage where it had free access to food and water at all times.

The baseline response rates for R12 varied from 20 to 75 responses per minute--a rather wide baseline base--prior to initiating the drug series (Figure 1). The last pre-injection session's data (i.e., 75 responses per session) indicated that R12 had attained a rapid and dependable response rate pattern on an FR20 Escape Schedule, with the probability of maintaining a high rate of response in subsequent sessions.

Following the establishment of the pre-injection baseline band, the injection period proper was begun. In this part of the procedure, the subject was run on an FR20 for approximately 10 minutes warm-up (i.e., the initial) prior to receiving a drug injection. The actual recorded experimental session was initiated by the intraperitoneal injection of the drug. The recording session lasted 50 minutes.

Injection procedures were based on the usual procedures (Thompson and Schuster, 1968). These included dosage calculations based on known LD 50 levels for gold thioglucose as reported by Wagner and DeGroot (1963) for the rat.

Following the establishment of the baseline, R12 was initially injected with 0.5 cc of sesame oil to screen for undesirable effects from the vehicle. The injection series for R12 consisted of the following injections of gold suspended in sesame oil, in which each drug injection session was followed by at least one or more non-drug-injection sessions, thus allowing for recovery of the baseland band

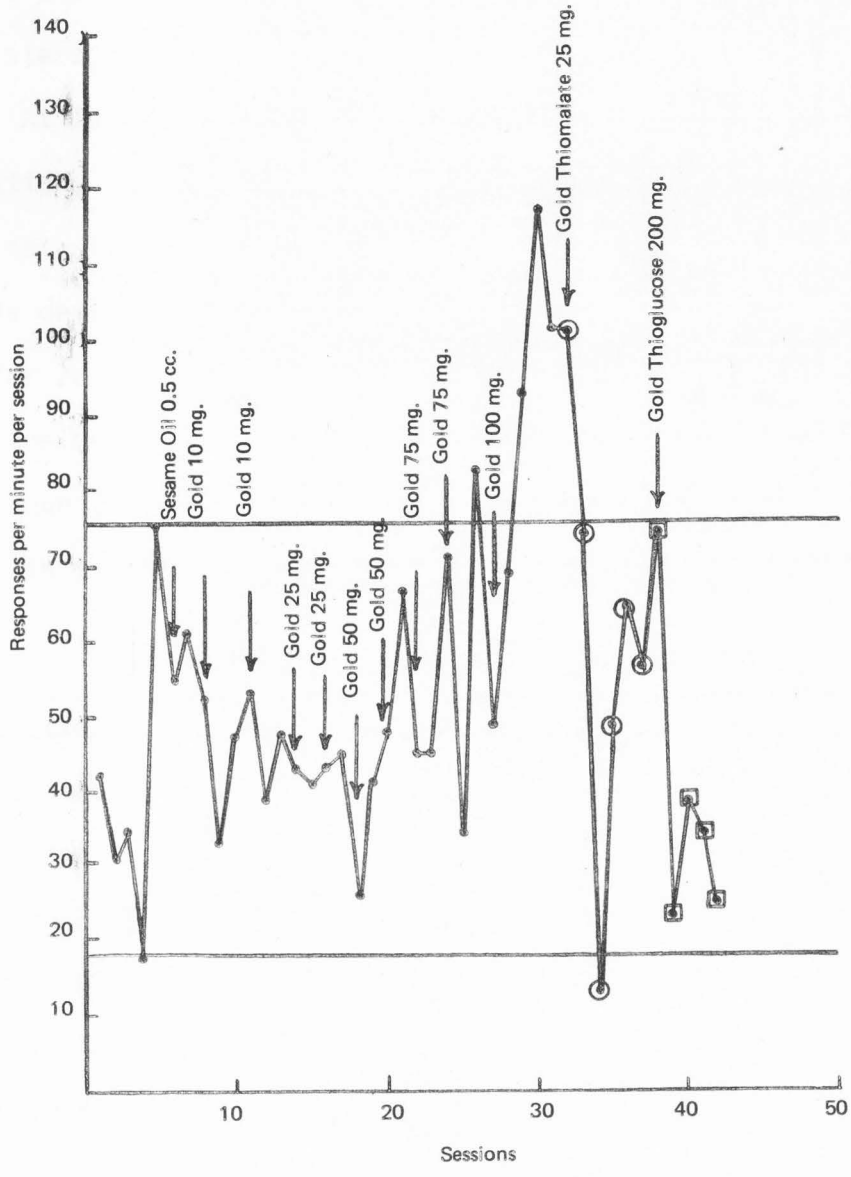


Figure 1. Subject R12 on FR20 escape schedule: responses per minute following administration of gold, gold thiomalate, and gold thioglucose.

response rate prior to injecting once again: 10 mg, 10 mg, 25 mg, 25 mg, 50 mg, 50 mg, 75 mg, 75 mg, and 100 mg. The subject was subsequently given a single 25-mg gold thiomalate injection. Following recovery of the baseline, a final 200-mg injection of gold thioglucose was administered and escape behavior was followed for several additional sessions. At least one or more recording session followed each drug administration, depending on whether the response rate departed from the baseline. The criterion vehicle which was used consisted of no appreciable deviation from the baseline band. The technique of allowing for recovery of the baseline after a drug injection and then repeating the procedure was followed. It is the intrasubject replication technique (Sidman, 1960) which increases the experimenter's confidence in the reliability of resulting data with few subjects.

Results

Calculations were made daily following the termination of an experimental session to determine the results of that session, and charted so that deviations from the baseline could be made apparent. Figures 1 and 2 represent the complete experiment for R12, as well as an indication of response rate deviations from the initial baseline and body weights of the pre-drug administration period.

It is apparent from the graphs that for all gold injections through session 27, rates of response were confined to the wide baseline band (Figure 1). The subject's response rates increased significantly above baseline levels following the last gold injection, increasing to over 100 responses per minute for several sessions.

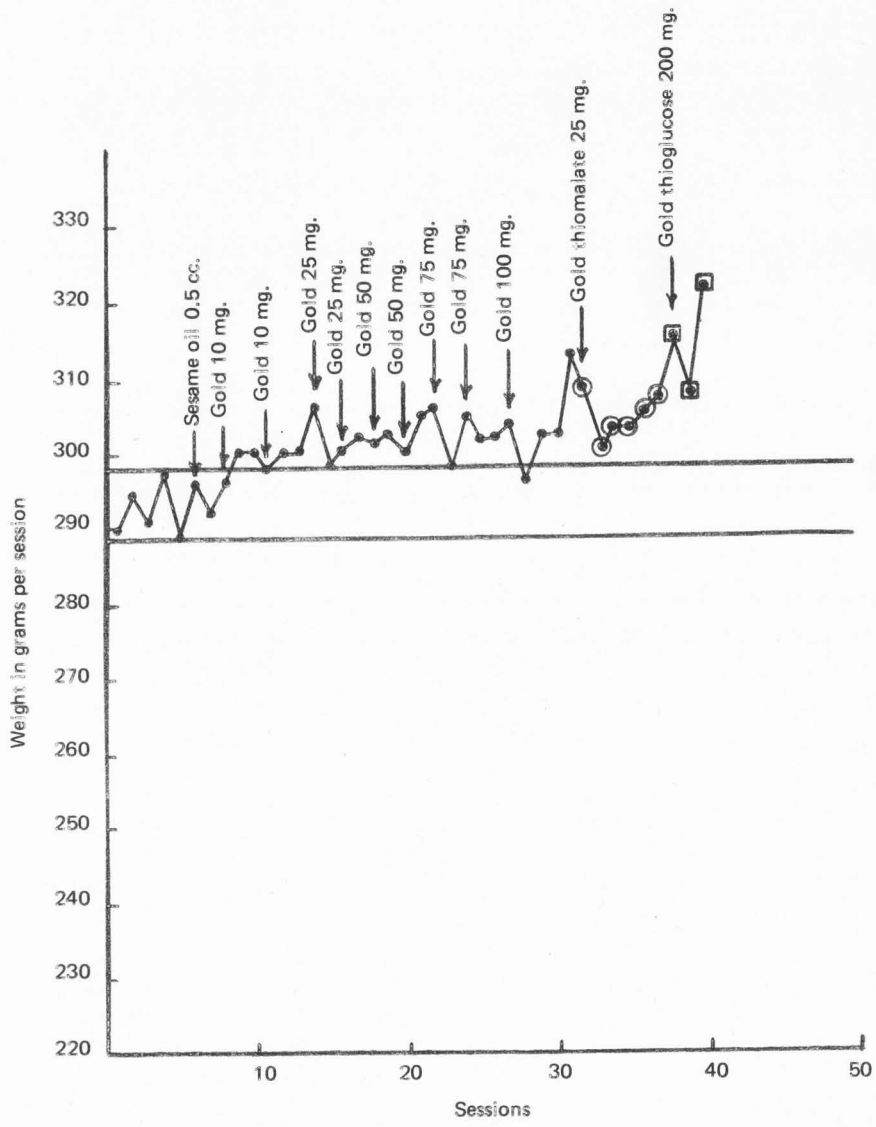


Figure 2. Subject R12 on FR20 escape schedule: weight fluctuations following administration of gold, gold thiomalate, and gold thioglucose.

R12 was subsequently injected with a single gold thiomalate injection of 25 mg. In the subsequent two sessions, response rates fell from over 100 to 13 responses per minute, the lowest rate in the experiment and well below the baseline band. Recovery to above baseline levels (i.e., 50-60) was noted in the subsequent three sessions. A final injection of 200 mg of gold thioglucose was administered to R12. Response rates fell to less than 30 responses per minute on two sessions (i.e., at the lowest rate within the baseline band) without achieving recovery at the termination of the experiment.

The response rate drops following gold thiomalate and gold thioglucose administration were quite significant, as at 15 or 20 responses per minute, qualitative changes in behavior are evident. Furthermore, no recovery from the gold thioglucose was evident at the termination of the experiment, indicating the possibility of permanent behavioral changes, associated with extensive hypothalamic damage as a result of the heavy 200 mg dose of gold thioglucose.

As for weight fluctuations (Figure 2), the general trend was toward a slight increase upward (i.e., from 290 to 320 gm), although a temporary large weight drop was observed following the 100 mg injection of gold, the 25 mg injection of gold thiomalate, and the 200 mg dose of gold thioglucose.

Discussion of results

Until the gold injection series had been completed, the general trend was quite misleading, for in checking Figure 1, it was evident that the baseline response rate was not altered by the gold injection series; i.e., the response rates for most of the sessions fell in the middle of the baseline band at around 40-50 responses per minute. In

the sessions following the 100 mg gold injection, however, the average daily response rate increased from an average of approximately 40 to 50 responses per minute to 100 or more responses per minute. It can be determined by graphic inspection in retrospect, that gold administration suppressed the response rate potential, as evidenced by release of suppression in the sessions following discontinuance of gold administration, in which response rates increased markedly, probably associated with detoxification processes.

The injection of 25 mg of gold thiomalate which followed the gold injection series was associated with a drop in response rate from an average of over 100 responses per minute to a low rate of 13 responses per minute. This decrement was followed by a recovery of response rate to the initial baseline rate four days following this gold thiomalate injection. It can be noted (Figure 1) that the decrease in response rate did not follow the administration of gold thiomalate during the drug injection session, although 24 hours later a drop in rate was quite evident.

The final 200 mg gold thioglucose injection did not affect response rate during the drug session, although in the following sessions the response rates fell to a low level. Baseline recovery rate did not occur prior to the termination of the experiment.

The temporary weight losses which were observed suggested that there were toxic effects due to the chemical compounds on either hypothalamic centers or other parameters of the animal's biochemistry.

A likely explanation for the apparent long-term suppression of behavior following gold thioglucose administration as opposed to the temporary suppression noted with gold might be related to the differential

biological distributions of the two compounds. In the case of gold, deposition is limited to abdominal organs. With gold thioglucose, the gold deposition is localized abdominally (Block, Buchanan, and Freyberg, 1942), as well as hypothalamically (Debons et al., 1962).

EXPERIMENT 2

Gold thiomalate (Myochrisne) is a drug which has been routinely used on humans and is, therefore, equally important as gold thioglucose from a medical point of view.

Method

Subjects

Three female rats (Long-Evans strain--R4, R5, and R10) were used in this experiment. They were three months old at the start of the sessions and were experimentally naive.

Apparatus

The same apparatus was utilized as described in Experiment 1.

Procedures

The same procedures were utilized as in Experiment 1 except for changes in drug dosages.

R4 and R5 were given identical dosages. Dosage schedule was as follows: vehicle injection, gold thiomalate 10 mg, 25 mg next day (for possible desensitization effects), then 10 mg, 25 mg, and 50-mg dosages. R10, on the other hand, was injected twice with gold thiomalate 10-mg dosages following the sesame oil control injection. Except for the combined 10-25-mg dose for R4 and R5 initially, all drug injections were followed by recovery of baseline prior to reinjection.

Results

The initial double dose of 10-25 mg of gold thiomalate was not

followed by departure from the baseline in R4 or R5. Consequently, a second dose of 10 mg of gold thiomalate was administered to the two subjects. In the case of R5, death occurred within 48 hours, which was preceded by a profound drop in rate on the last session. Response rates dropped extremely below the baseline band of 30-45 responses per minute for the five preceding sessions (Figures 3 and 4). R4's record was quite similar to that of R5's, but subsequently, recovery of the baseline rate occurred. R4 was next injected with a 25-mg dose of gold thiomalate. Baseline recovery took almost two weeks following this 25-mg injection. A final 50-mg dose of gold thiomalate resulted in a decreased rate from which the animal failed to recover its baseline activity prior to termination of the experiment (Figures 5, 6, and 7). In the case of R10 (the third thiomalate subject), a single 10-mg gold thiomalate injection depressed rates of responding for nearly two weeks before recovering the original baseline rate. A second 10-mg gold thiomalate dose was injected into R10 with no apparent baseline recovery at termination of the experiment (Figures 8 and 9).

As for weight fluctuations, the striking similarity in curves for weight loss and response rate drops for all three gold thiomalate subjects (i.e., R4, R5, and R10) indicates that there is a high probability that toxic abdominal effects from the gold thiomalate may contribute primarily to the response rate decrease in gold thiomalate-injected subjects. Also, response rate decrememts are demonstrable for weeks or longer following a gold thiomalate injection, thus indicating the long-term toxic effects. Finally, tolerance is indicated by the larger dosages (e.g., 50 mg) being tolerated (e.g., R4) without pronounced toxic reactions visible.

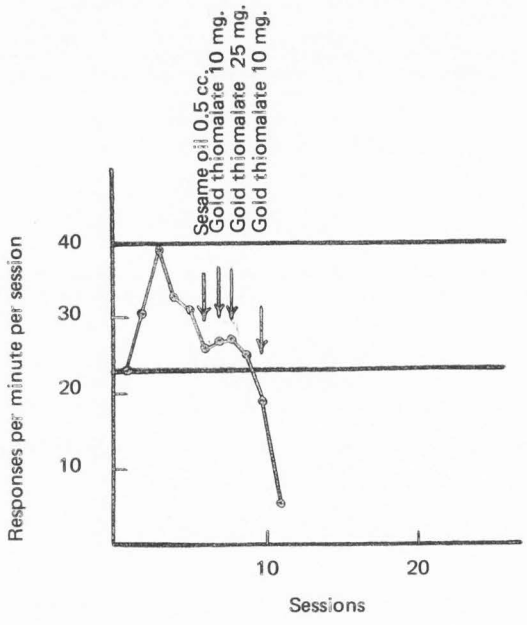


Figure 3. Subject R5 on FR20 escape schedule: rate of responses per minute over sessions following three gold thiomalate injections.

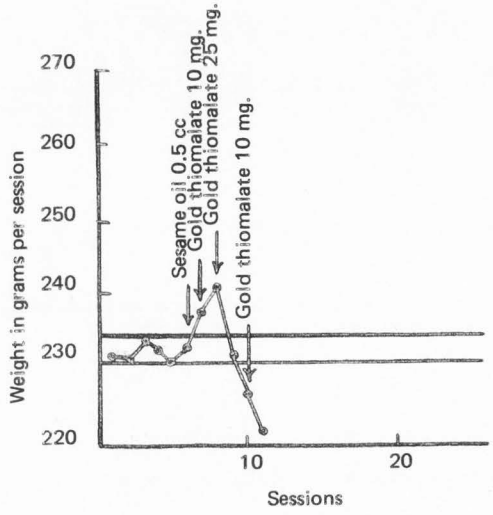


Figure 4. Subject R5 on FR20 escape schedule: weight fluctuations over sessions following three gold thiomalate injections.

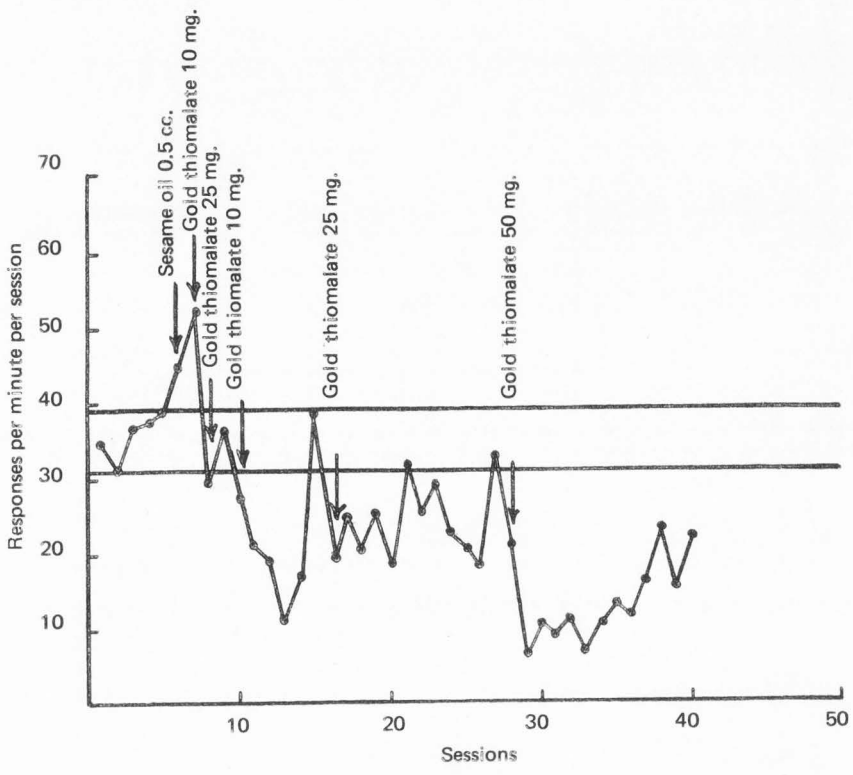


Figure 5. Subject R4 on FR20 escape schedule: responses per minute following administration of gold thiomalate in increasing dosages.

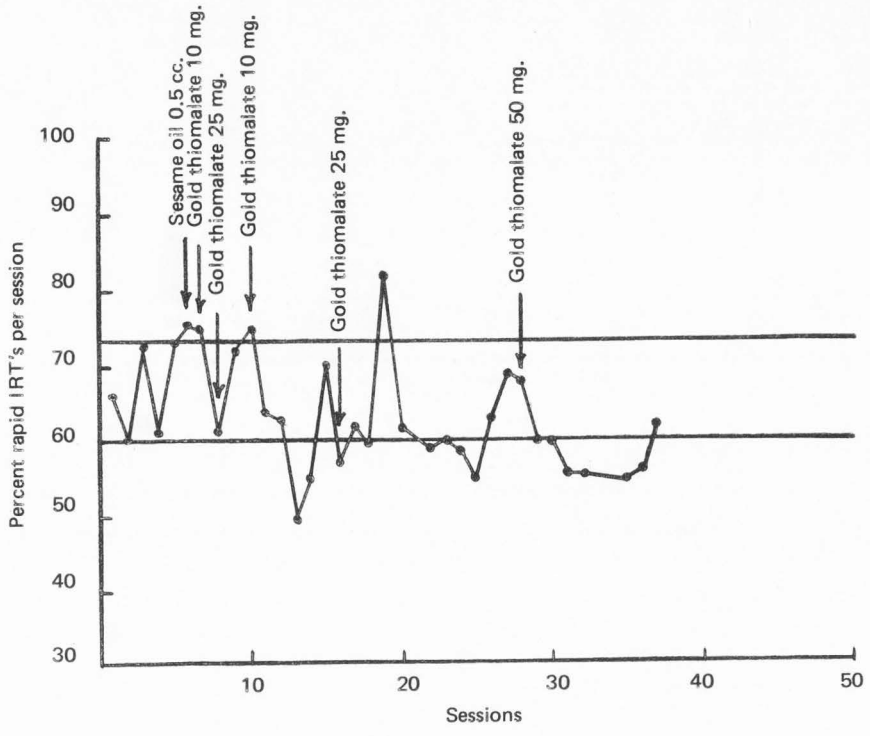


Figure 6. Subject R4 on FR20 escape schedule: per cent rapid IRT's over sessions following administration of gold thiomalate in increasing dosages.

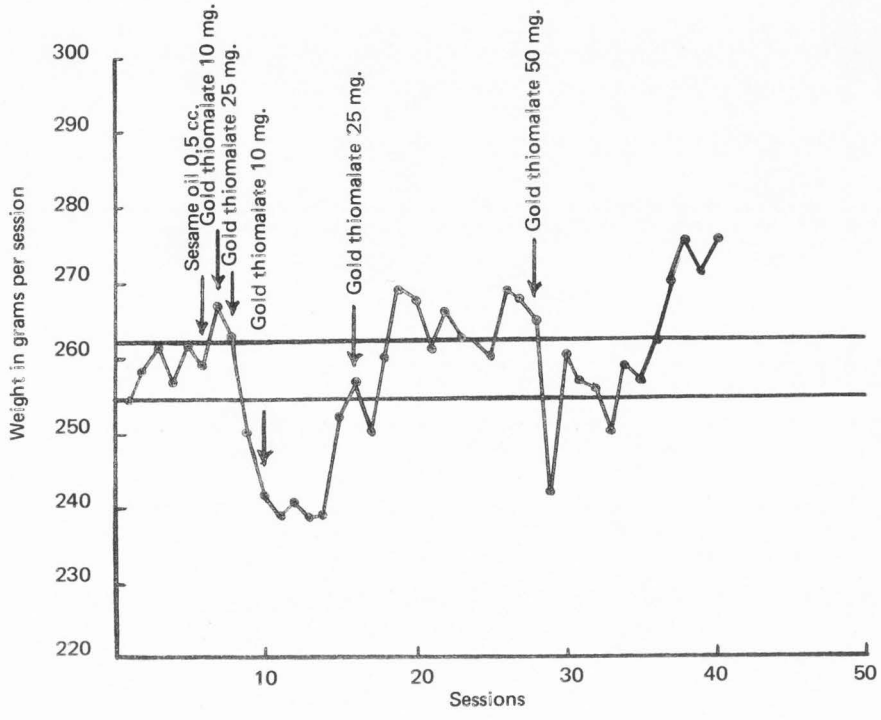


Figure 7. Subject R4 on FR20 escape schedule: weight fluctuations over sessions following administration of gold thiomalate in increasing dosages.

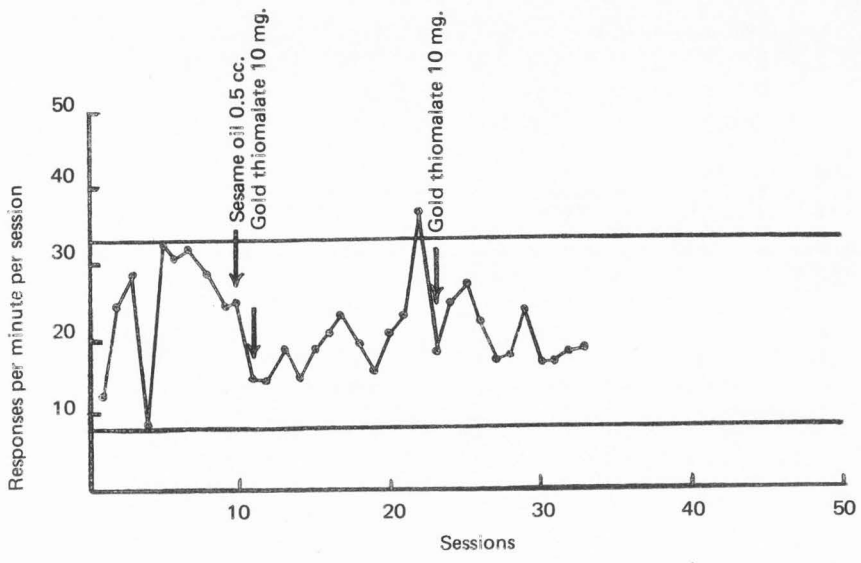


Figure 8. Subject R10 on FR20 escape schedule: responses per minute following administration of gold thiomalate in increasing dosages.

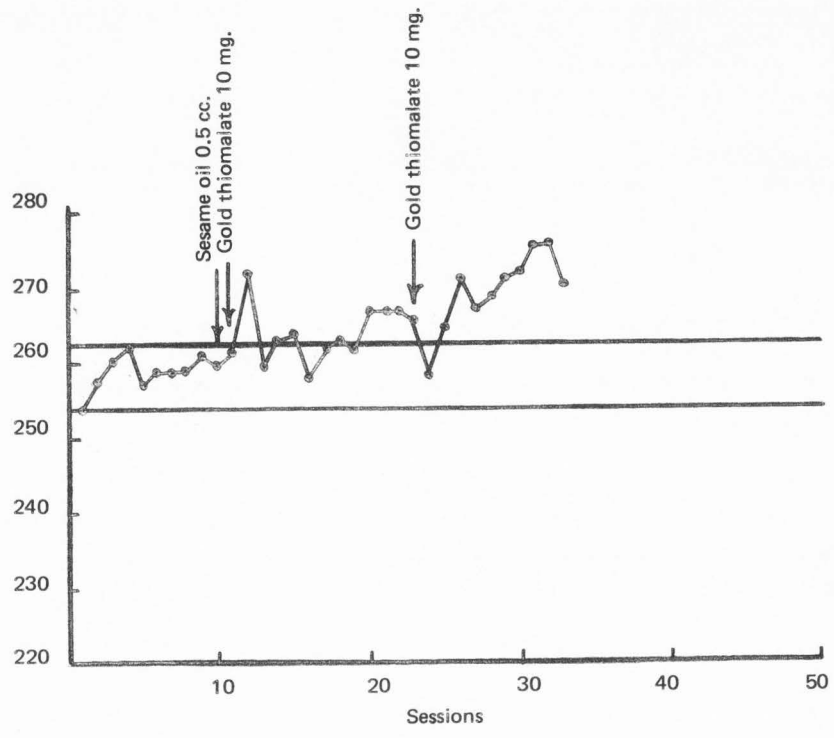


Figure 9. Subject R10 on FR20 escape schedule: weight fluctuations over sessions following administration of gold thiomalate in increasing dosages.

Discussion of results

Because of the high solubility and partial ionic state of the gold thiomalate, the investigator attempted to "desensitize" animals R4 and R5 with an initial 10-mg dose followed by a 25-mg dose the following day. This could be considered to be a prolonged 35-mg injection, from a conservative point of view. The data from Figures 3 through 7 indicate that following combined gold thiomalate injections, response rate did not fall off on the following session (i.e., the baseline band response rates for R4 and R5 were maintained). Consequently, an additional 10-mg dose followed for both R4 and R5. Within 48 hours, R5 died, but R4 survived, although response rate dropped drastically for both subjects. Consequently, a rough LD 50 (i.e., lethal dose for half the number of subjects) could be put at about 35 mg, or 0.15 mg per gram of body weight for gold thiomalate in mature Long-Evans female rats.

Fast interresponse times (IRT's) generally corresponded (Figure 6) with a rapid response rate, indicating that no great change had occurred in non-responding while the shock treatment was on. It can be noted that from a mathematical point of view, should a reversal occur for fast IRT's (i.e., high per cent of fast IRT's with a low response rate per minute), then the conclusion reached would be that non-responding is increasing at a disproportionately high rate (i.e., if per cent of fast responses is high while overall response rate is low, the few slow responses must be very long).

As for weight changes, in the case of R4 the weight chart closely parallels the response-per-minute chart, indicating a relation between the assumed index of toxicity (i.e., weight loss) and the associated

response behavior (i.e., drop in response rate). The relation should not be considered as exact, since the operant response of eating is not likely to be perfectly related to the loss of the reinforcer's (food) strength from liver toxicity, brain effects, or other biological concomitants.

It can be concluded from these data that injections of gold thiomalate are followed by a large drop in response rate as well as rapid weight loss within 24 to 48 hours following administration, although eventual recovery of baseline may be noted. A fourth subject (R12) had also received a gold thiomalate injection (25 mg) (see Experiment 1) with similar results. As gold thiomalate administrations are repeated, the tendency toward drug tolerance in rats can be inferred from the data.

EXPERIMENT 3

Gold thioglucose is not only important because it is a medical therapeutic agent in rheumatoid arthritis (i.e., Solganol), but lesions produced in the VMN of the mouse hypothalamus (Marshall, Barnett, and Mayer, 1955) have opened up a new avenue of behavioral and physiological research into obesity resulting from overweight, overeating, and associated emotional changes.

Method

Subjects

Four three-month-old female Long-Evans rats (R7, R9, R11, and R6) served as the subjects for this experiment. They were naive prior to the experiment.

Apparatus

The apparatus used in this experiment was the same as for Experiments 1 and 2.

Procedures

Procedures were the same as in the previous experiments, except for drug dosages, which were individualized--not only because of subject variability, but also because of the different schedules and baseline rates. (The subject of schedule effects has been considered in an earlier section.)

R9 was a rapid FR20 responder (i.e., baseline band of 80 to 100 responses per minute). R7 was a medium-rate responder on a fixed ratio

of 20 (i.e., from over 40 to over 50 responses per minute baseline band). R11 and R6 were on an FR12 Escape Schedule, both stabilized on a fairly low response rate (i.e., 10-20 responses per minute for R6 and 20-30 responses per minute for R11's baseline level). The drug dosages for each subject are indicated in the graphs (i.e., Figures 10 through 21).

A return to baseline activities was attained in the majority of the sessions. Higher dosages of the drugs were given when activity was below the established baselines to study effects of increasing dosages when baseline recovery was practically unachievable without attempting retraining procedures.

Results

After the establishment of the high response rate baseline for R9, the injection series was initiated. Following the control injection of 0.5 cc of sesame oil, a combined 10-25-mg gold thioglucose dosage was given to provide for desensitization should sensitivity be involved. A profound drop in response rate occurred (i.e., down to approximately 60 responses per minute per session), which remained below the baseline band for three sessions. This was followed by a recovery of the initial baseline. A second 10-mg dose was administered to R9, which also brought the rate down to approximately 60 responses per minute (Figures 11 and 12) prior to once again attaining the baseline. This was followed by a series of double 25-mg and 50-mg injections without any drop below the baseline band. The final 50-mg gold thioglucose dose was associated with a drop in rate to 60 responses per minute, well below the baseline band. After nine days without recovery of the baseline, the subject was injected with 150 mg of gold thioglucose to study the effects of a much heavier drug administration. Following

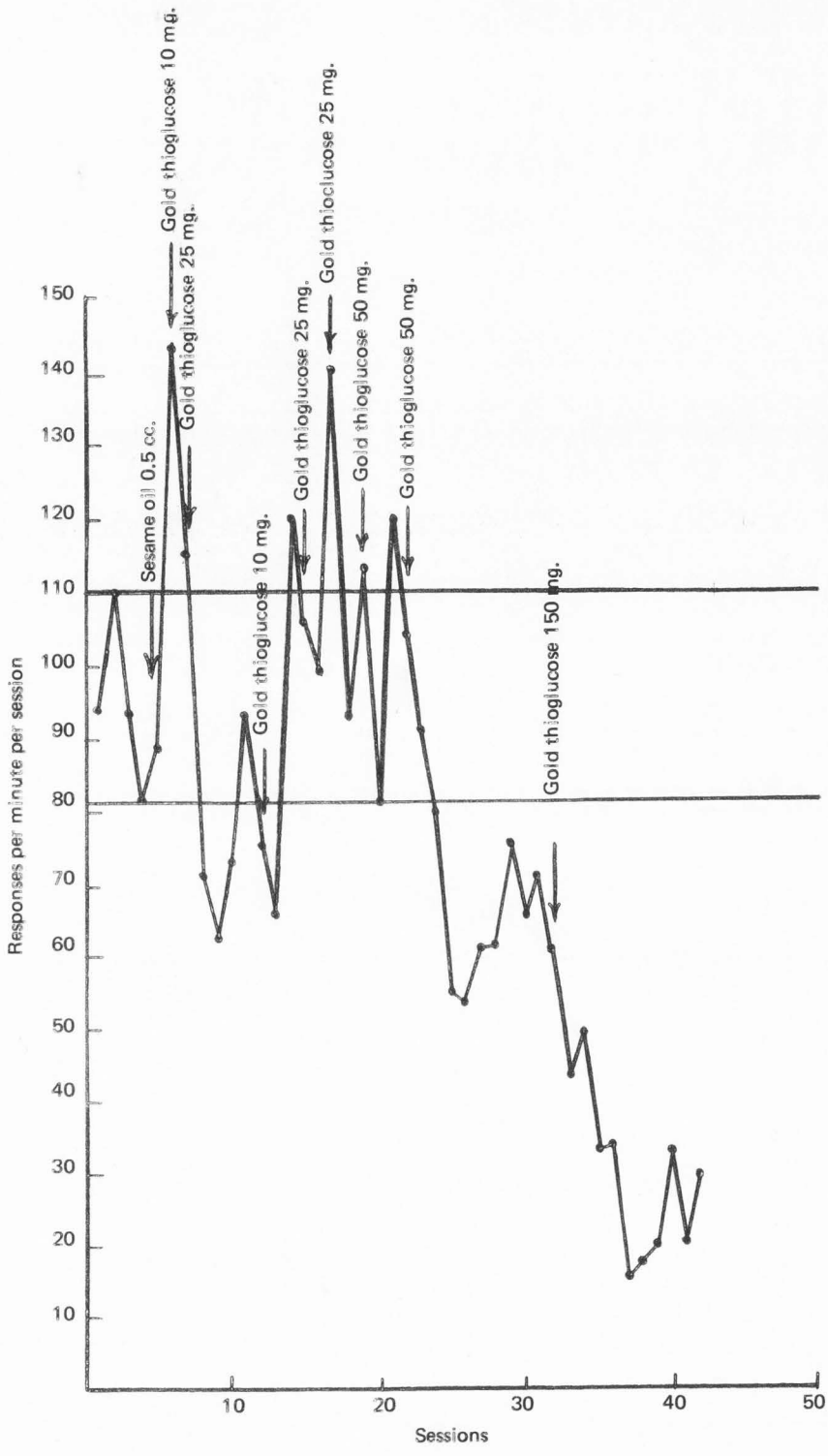


Figure 10. Subject R9 on FR20 escape schedule: responses per minute following administration of gold thioglucose in increasing dosages.

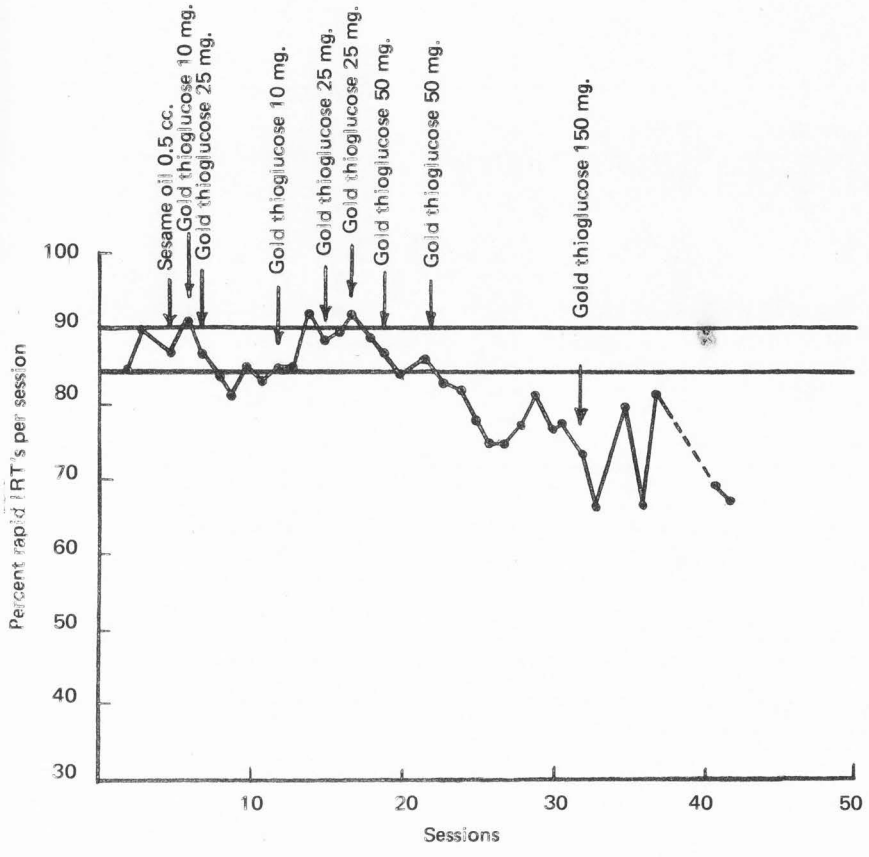


Figure 11. Subject R9 on FR20 escape schedule: per cent rapid IRT's over sessions following administration of gold thioglucose in increasing dosages.

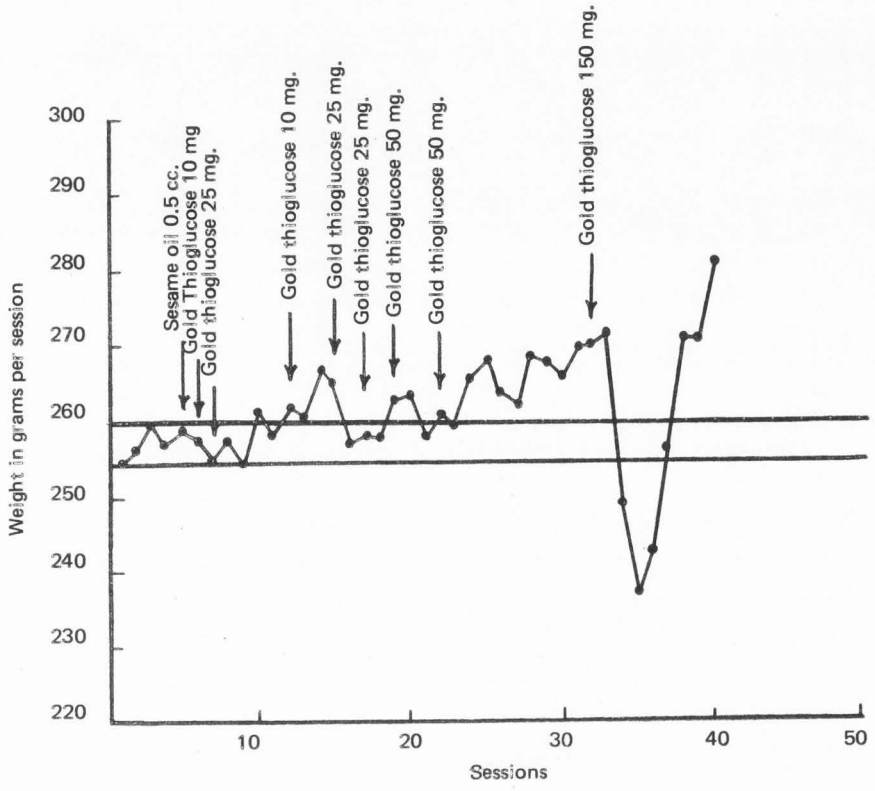


Figure 12. Subject R9 on FR20 escape schedule: weight fluctuations over sessions following administration of gold thioglucose in increasing dosages.

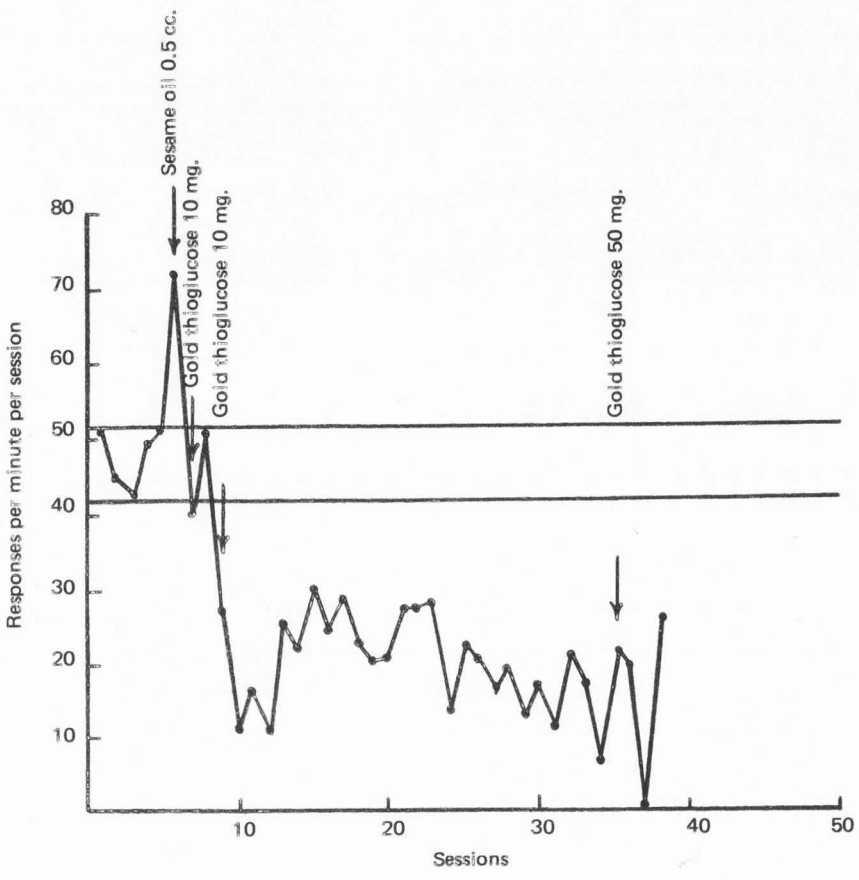


Figure 13. Subject R7 on FR20 escape schedule: responses per minute following administration of gold thioglucose.

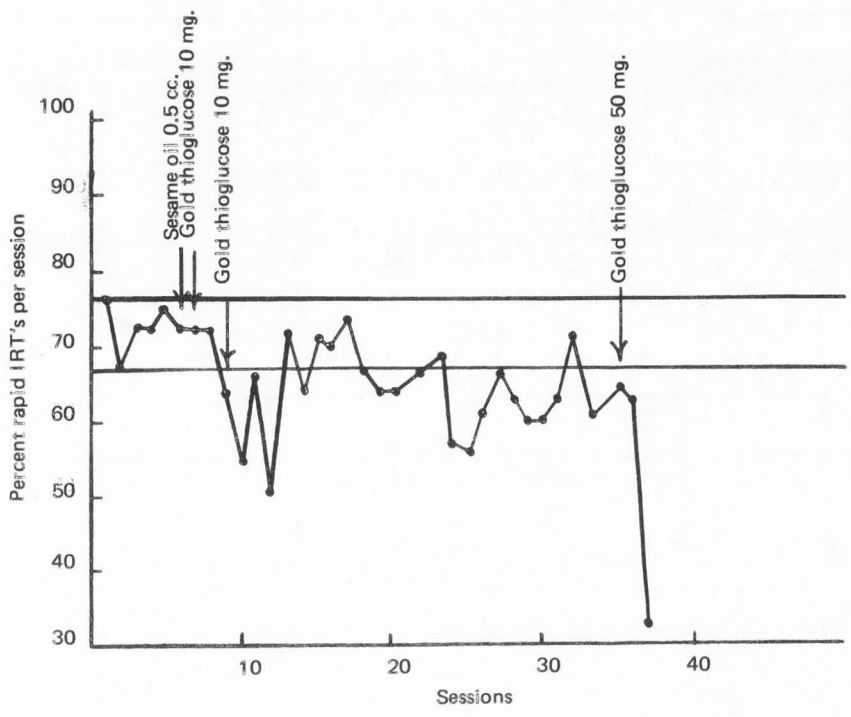


Figure 14. Subject R7 on FR20 escape schedule: per cent rapid IRT's over sessions following administration of gold thioglucose.

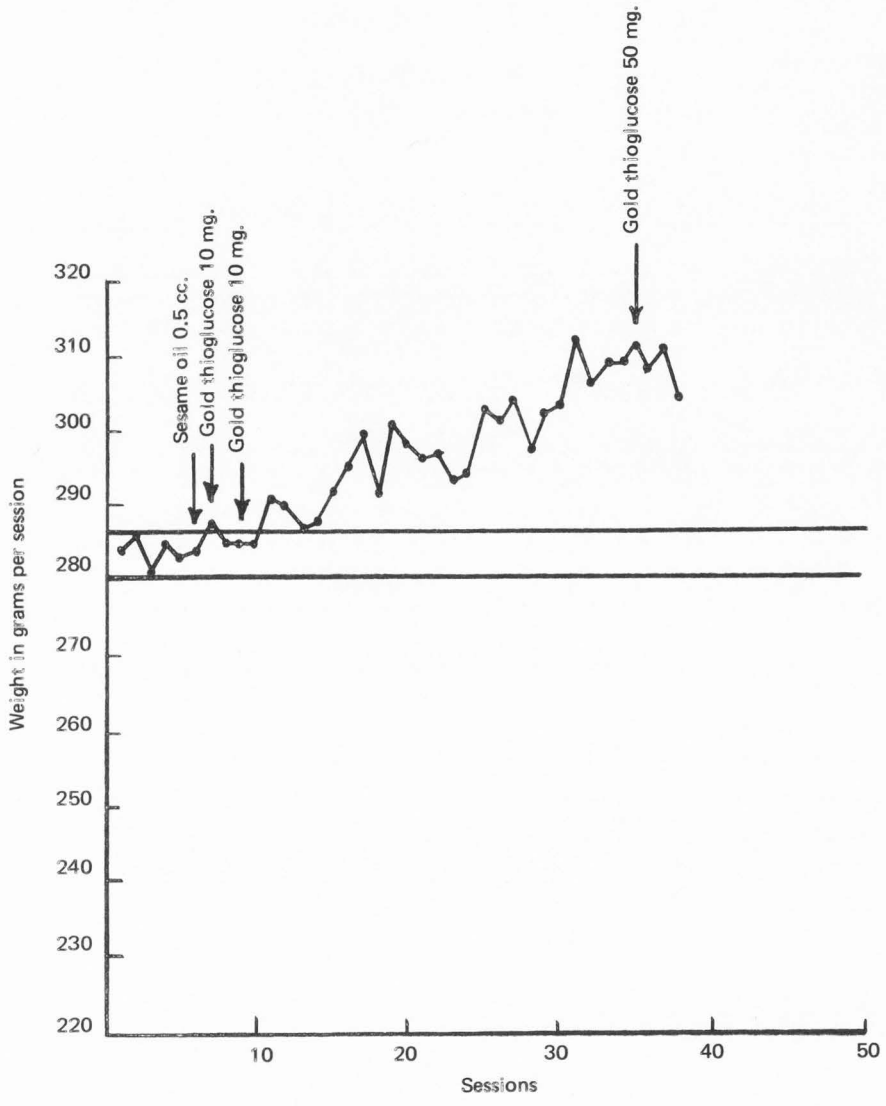


Figure 15. Subject R7 on FR20 escape schedule: weight fluctuations over sessions following administration of gold thioglucose.

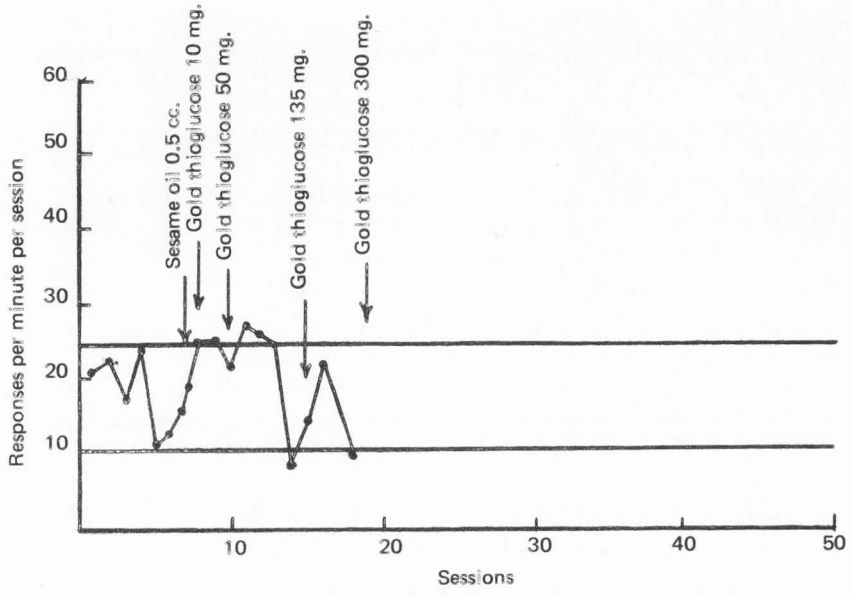


Figure 16. Subject R6 on FR20 escape schedule: responses per minute following administration of gold thioglucose in rapidly increasing dosages.

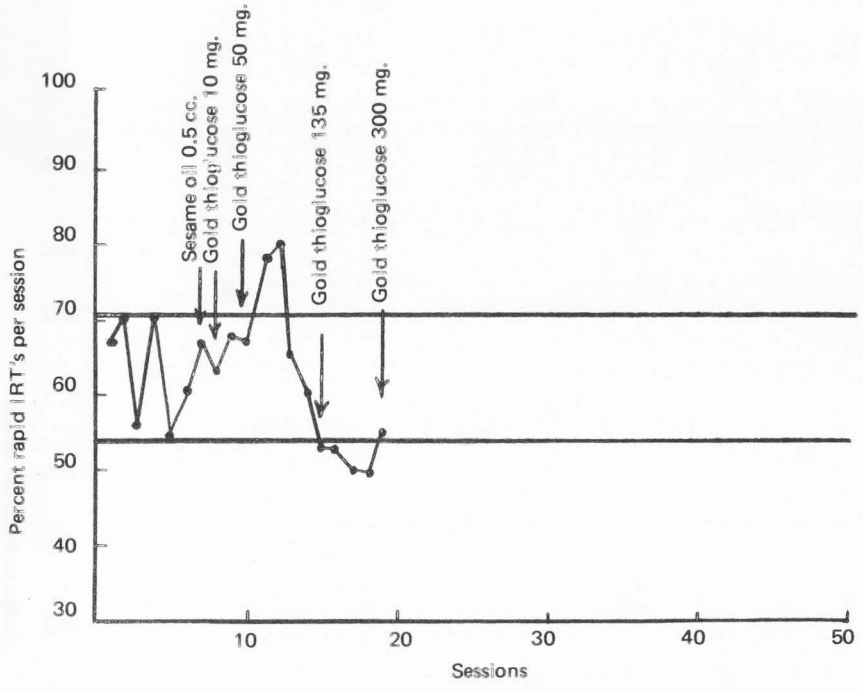


Figure 17. Subject R6 on FR20 escape schedule: per cent rapid IRT's following administration of gold thioglucose in rapidly increasing dosages.

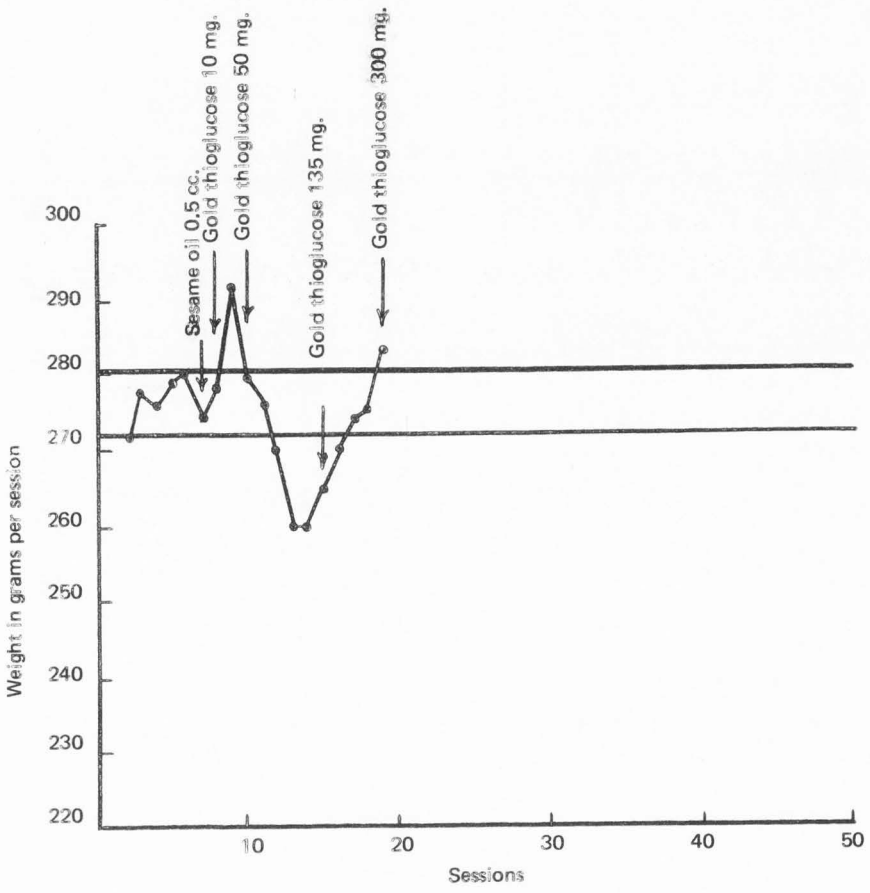


Figure 18. Subject R6 on FR20 escape schedule: weight fluctuations over sessions following administration of gold thioglucose in rapidly increasing dosages.

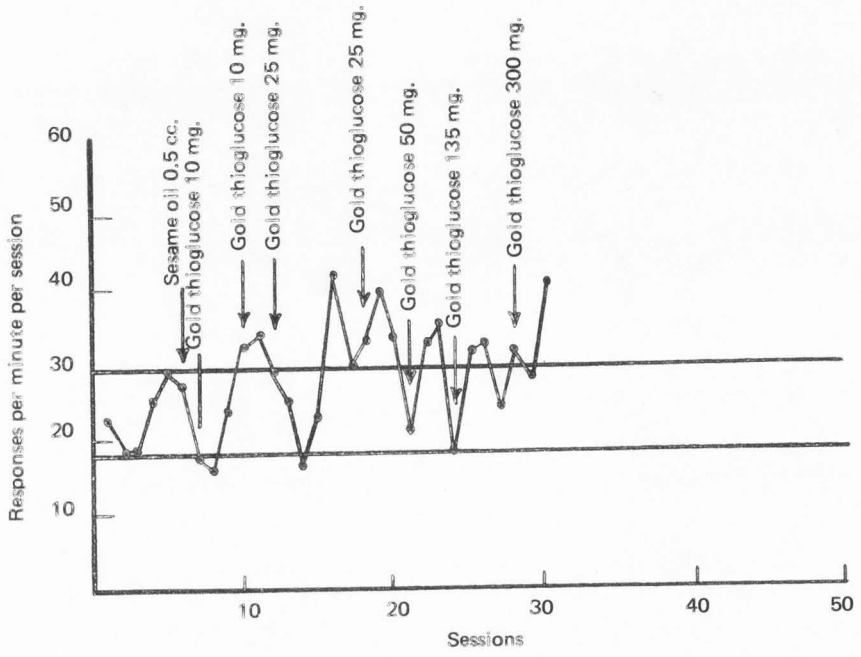


Figure 19. Subject R11 on FR12 escape schedule: responses per minute following administration of gold thioglucose in gradually increasing dosages.

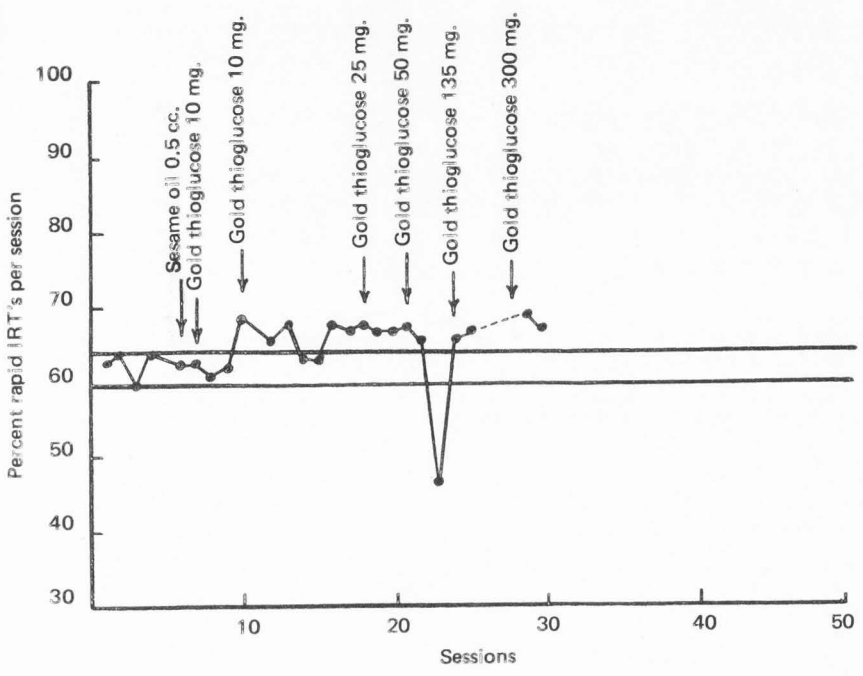


Figure 20. Subject R11 on FR12 escape schedule: per cent rapid IRT's following administration of gold thioglucose in gradually increasing dosages.

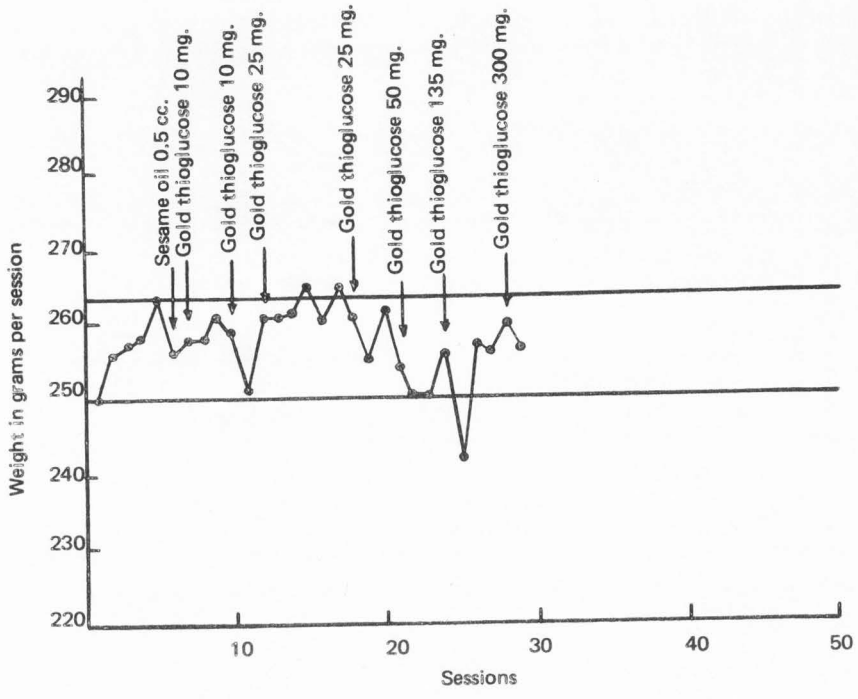


Figure 21. Subject R11 on FR12 escape schedule: weight fluctuations following administration of gold thioglucose in gradually increasing dosages.

this injection, response rates dropped much lower, resulting in almost complete deterioration of the fixed ratio behavior, in contrast to the high and stable response rates evident two weeks previously for R9. Weight fluctuation data for R9 is quite significant in its lack of correspondence with response rate data. Although weight drops are evident following some of the heavy gold thioglucose dosages, weight recovery is quite complete within several sessions, in contrast to the absence of response rate recovery for the gold thioglucose. For example, following the 150 mg gold thioglucose administration, response rates dropped drastically with no apparent recovery; while weight losses--although falling far below the baseline--were recovered, resulting in the highest final weight recorded during the experiment for R9.

Following the vehicle injection into R7 (Figures 13, 14, and 15), a 10-mg dose of gold thioglucose was given the animal. R7's response rate did not fall below the established baseline based on the following session. Consequently, a second 10-mg gold thioglucose injection was administered. The rate dropped as a result of the treatment. Since the original baseline was not reestablished, after two weeks the animal was injected with a 50-mg gold thioglucose dose to note behavioral effects superimposed upon an activity level below the baseline response levels. No substantial response rate changes in the direction of baseline recovery were noted prior to the death of the subject.

R6 (Figures 16, 17, and 18) received a vehicle injection, a 10-mg gold thioglucose injection that was followed by a 50-mg, 135-mg, and finally a 300-mg gold thioglucose injection. After this treatment, an anaphylactic reaction occurred and death ensued. Wide fluctuations in response rate were noted throughout the experiment with R6 (i.e., both

increases and decreases in rate following administration of the drug, almost totally within its baseline band of 10-25 responses per minute).

For R11 (Figures 19, 20, and 21), which was on an FR12 escape schedule and had a low rate of 10 to 25 responses per minute for its baseline band, an inconsistent response pattern, within baseline limits, was recorded.

For all four subjects, weight fluctuations were relatively minor (Figures 12, 15, 18, and 21), except for the large weight drop following the 150-gm gold thioglucose injection into R9 and the 135-mg injection into R11.

Discussion of results

In the case of R9, a rapid drop in response rate was demonstrated following the first 10-25-mg gold thioglucose injection. There was a subsequent recovery of baseline rates. A second phase of relative stability of response rates followed, and this was associated with a number of increasing dosages of gold thioglucose administrations. The most likely explanation for the observed stability was the development of tolerance. Subsequent deterioration of response rate without a continuation of additional injections points to the possibility for cumulative toxic effects which overcame the organism's tolerance capacity.

R7's rapid deterioration of response rate could be attributed to the "strained" character of its response behavior--recognized in the intermediate baseline response rate of approximately 40 to 50 prior to drug injection--and to subsequent toxicity noted in the observation of tremors development following the 50-mg gold thioglucose injection.

Subsequent lethal effects point to the particular sensitivity of R7 to gold thioglucose.

R6 and R11 had stabilized at a low rate of response (i.e., 10-30 responses per minute) with a relatively short ratio (i.e., 12), and were not subsequently appreciably affected by gold thioglucose injections. This effect was probably due to both the ease of responding at low rates on a short ratio, and possible tolerance development to the increasing dosages. No decrease in response rate over several sessions was noted in the case of R11. Schedule effects did correspond with Winogard's (1965) predictions; i.e., greater stability associated with drug effects with subjects trained under short fixed ratios.

Furthermore, lack of pronounced weight fluctuations, except following very heavy dosages of gold thioglucose, point to the relatively less toxic nature of gold thioglucose in comparison with the large weight fluctuations following gold thiomalate injections.

The major differences between gold thioglucose and gold thiomalate were that weight losses were associated with the injection of gold thiomalate following most drug administrations, but with gold thioglucose injections, only the heavier dosages affected body weight significantly. Also, when both short and long fixed ratios were considered, as well as response rates associated with the ratios in all subjects, it is evident that gold thiomalate injections were always followed by decrease in response. In the case of gold thioglucose, rate decrements generally accompanied only the heavier dosages and then only in strained ratio conditions. For example, R11, on a low-rate FR12 ratio, was not appreciably affected by the 300-mg gold thioglucose dose; while in the case of the strained character of R7's response record--an intermediate

response rate subject--gold thioglucose drug administrations were followed by a definite downward trend in response rates.

EXPERIMENT 4

In 1960, Mayer stated that although rats can be injected with heavy gold thioglucose dosages compared to mice (i.e., 1 mg per gram of body weight), and hypothalamic lesions consequently form, the rat does not survive the toxicity and consequently cannot become obese as is the case in approximately 50 per cent of injected mice.

Method

Subjects

Six rats served as subjects for this ethological study. Three were male Long-Evans rats, over three months of age. The other three subjects were female Long-Evans rats which had been run on escape schedule procedures and administered gold thioglucose injections prior to the final part of the study.

Equipment

In this investigation, injections required the utilization of syringes. Weighing was by means of a balance, accurate to the nearest 0.1 gram.

Procedures

The three male rats were injected with 1.0 mg per gram of body weight of gold thioglucose. R1, the fourth subject (female), was injected as follows: 10 mg on a morning session, 50 mg 48 hours later, 145 mg 96 hours later, and 300 mg 96 hours later. Three hundred mg corresponded to over 1.0 mg per gram of body weight for R1. (See Figures 22 and 23.)

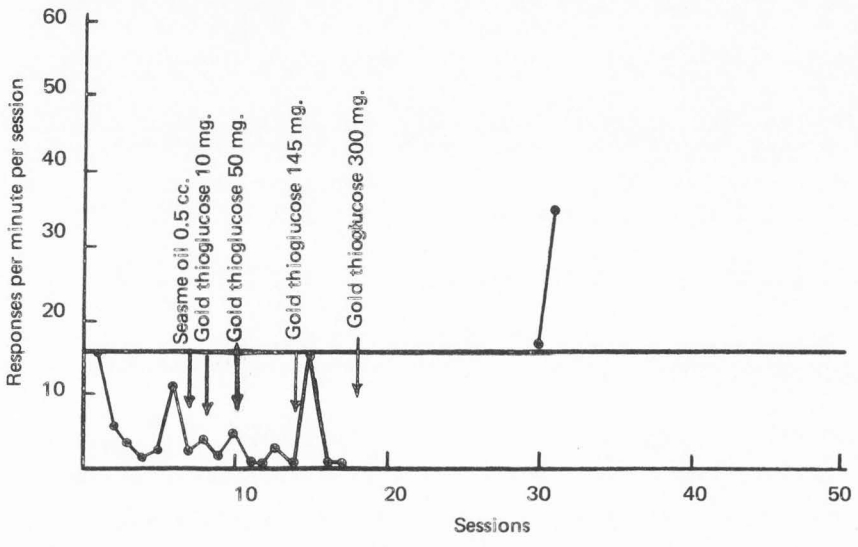


Figure 22. Subject R1 on FR20 escape schedule: responses per minute following administration of gold thioglucose in increasing dosages.

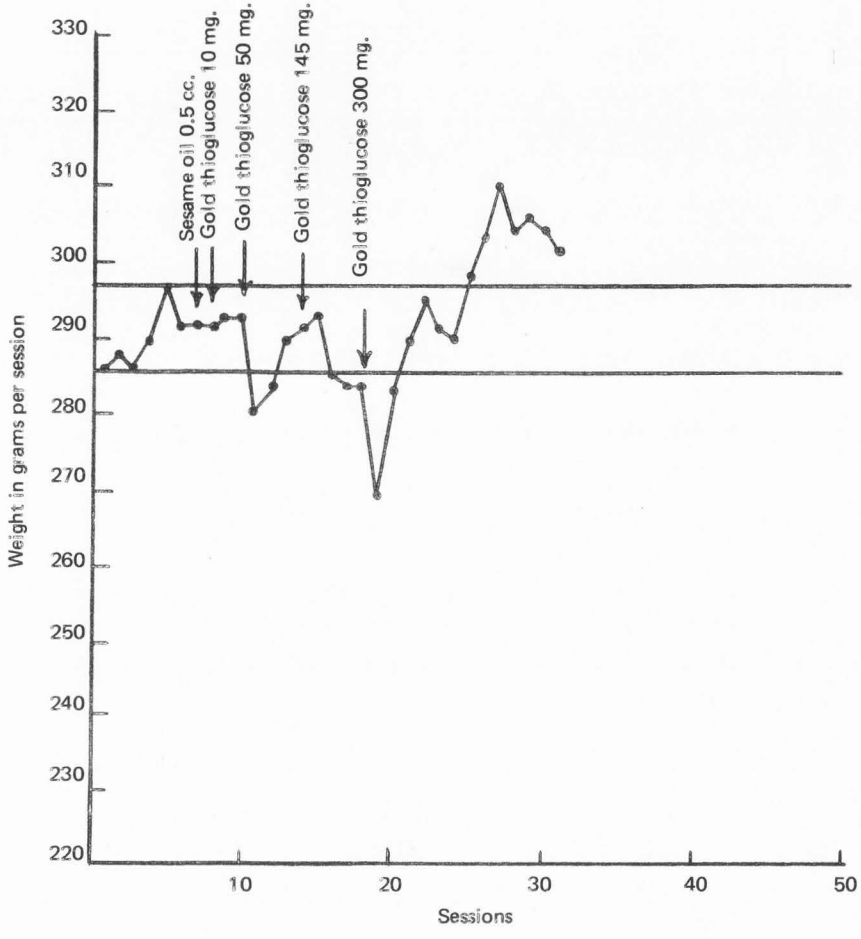


Figure 23. Subject R1 on FR20 escape schedule: weight fluctuations following administration of gold thioglucose in increasing dosages.

R6 (female) was injected in the same dose and interval (i.e., as R1) between drug injection series. R11, the sixth subject, was injected in graduated gold thioglucose injections, which included the following dosages: 10 mg, 25 mg, 50 mg, 135 mg, and 300 mg.

Results

The three male rat subjects were dead in their cages on the following morning. This phase of the experiment replicated Mayer's (1960) finding; i.e., that a single 1 mg per gram of body weight injection of gold thioglucose is fatal to rats.

R1's progress can be seen in Figure 22. The subject survived the very heavy dose of 1.0 mg per gram of body weight, thus providing the basis for rat hyperphagia and consequent obesity (Mayer, 1960). Within the first 10 days after treatment, no large weight increases were noted for R1. A weight reduction was noted on the first day following the 300-mg injection, but recovery was complete in several days, with no obesity. Following experimental session resumption, response rates increased above the baseline levels (Figure 22).

R6 died within two minutes after the 300-mg injection, with symptoms indicative of an anaphylactic reaction. R11 survived the initial 300-mg dose and completed the requirements of the FR12 escape schedule for that day (i.e., 50 minutes of operant responding). It also survived the 300-mg injection and maintained its operant behavior on the following days, prior to the termination of the experiment.

Discussion of results

In relation to the massive final gold thioglucose injection, indications of drug toxicity based on weight loss were minimal. R1 and R11

survived the 300-mg dosage of gold thioglucose. By developing tolerance to the drug, it would appear that much heavier dosages of gold thioglucose can be injected into a rat.

It is possible that since the data for Rl and Rll establish a precedent for a probable increase in the tolerance for gold thioglucose in rats, increases in the size of the hypothalamic lesions, as well as behavioral changes, may be expected in rats. With these dosages, similar lesions and behavioral changes may occur in higher species.

Rl, which initially failed to respond to shock, responded at a relatively high rate following the 300-mg gold thioglucose injection, possibly due to neurological alterations which affected the behavioral sets (Figure 22), thus allowing for greater flexibility of response, possibly associated with changes in drive states.

ADDITIONAL OBSERVATIONS

Gold Thioglucose and the Anaphylactic Response

A most interesting phenomenon that impinges on physiology and behavior both is the anaphylactic reaction--sometimes fatal--and the lesser reactions which seemingly stem from the same cause. Luparello, Stein, and Park (1964) investigated the possibility that following hypothalamic damage (and, consequently, likely autonomic malfunctioning), a decrease in anaphylactic reactions might result in hypothalamically-damaged rats. Positive results were obtained.

Method

Subjects

Two rats of the Long-Evans strain served as the subjects. The control subject was a normal non-injected animal. The experimental subject, R13, was a rat which had been injected with 40 mg, 70 mg, and 100-mg dosages of gold thioglucose within a 72-hour period approximately four months prior to the experiment.

Materials

The sensitizing drug for the experiment was sodium levothyroxine. Egg white was the protein made available for injections.

Procedures

Although the problem of developing an anaphylactic reaction in the

rat is fraught with difficulties, particularly as rats are quite resistant to anaphylactic shock (Sanyal and West, 1958), the method of sensitization found successful by Leger (1947) was attempted. The two subjects were first injected with 0.15 cc of egg white. During the following 12 days, the two subjects were tube-fed the 100 gamma of sodium levothyroxine and were otherwise on free feed. At the end of the 12-day sensitization phase, each subject was injected with 0.3 cc of egg white.

Results

No immediate reactions were noted. Within 90 minutes, the feet, as well as the area surrounding the mouth, of the normal rat swelled extensively. In the case of the experimental rat, no such swelling appeared to occur.

Discussion of results

Although the investigator considered the total procedure to be of an exploratory nature, rather than quite reliable, the swelling noted with the normal rat and absent in the gold thioglucose-injected rat points to the possibility that hypothalamic-lesioned tissue of the experimental animal may have been causally related to the supporting mechanisms for anaphylactic reactions. The possibility of a successful replication of such phenomena would lead to a technique of studying neurological contributions to allergic conditions.

Balance Beam Apparatus

Nineteen categories describing rat behavior were arbitrarily developed prior to the initiation of the experiment. In the sessions

prior to the establishment of a relatively stable baseline, it was noted that some of the proposed categories did not correspond to the observed behavioral traits. Furthermore, a gradual reduction in the initially observed behavior was evident in later sessions that preceded drug administration.

The subjects were the same rats run on the escape operant procedures, including R1, R6, R7, and R9 with gold thioglucose; R4, R10, and R5 on gold thiomalate injections; and R12 on all three (i.e., gold, gold thioglucose, and gold thiomalate).

Subjects were repeatedly placed on the beams for a total count of five times (Figure 24), after which they were observed for the balance of the allotted three minutes. All observations were recorded daily on the mimeographed sheets (see Appendix), including weight of the subject which was obtained by weighing each animal prior to placements on the beam apparatus. Individual observations of each subject were made daily by this procedure.

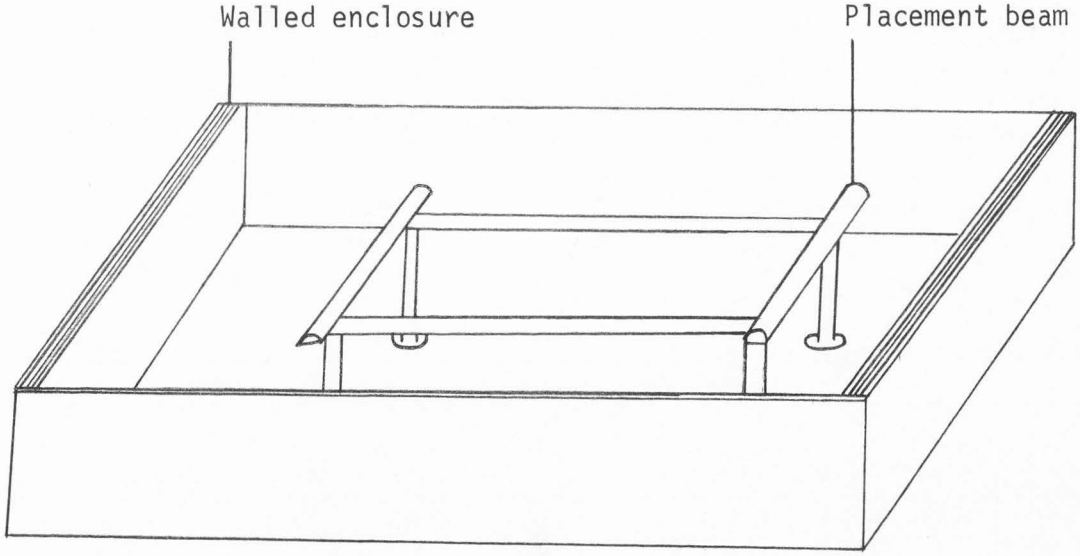


Figure 24. Balance beam apparatus.

Data were subjected to a statistical analysis, utilizing per cent frequencies (see Appendix Table 1). Baseline behavioral activities in per cent of occurrence (based on the last 10 days prior to initiating drug injections) were compared with post-baseline drug-injected sessions following. In this study, subjects served as their own controls.

A statistical analysis of the data indicates that mobility on the high beam (see Appendix, number 5), return to beams (number 12), and climbing on beam apparatus enclosure (number 19) distinguished baseline behavior from drug sessions. Activities of the above categories decreased for most of the subjects. Also the time for remaining on beam (number 18) following placements on the beam was a useful criterion, as time on the beam increased following drug administrations.

The most likely explanation for the above results is that difficult motor activity, such as is represented in numbers 5, 12, and 19, is reduced in frequency following abdominal and possibly neurological alterations in subjects, as well as overall reduction in movement (number 18). As for weight fluctuations throughout the several experiments (see Appendix Table 1), eight of the nine subjects gained only 5.5 gm from age three months at the initiation of the experiment, through the drug and post-drug injection experimental sessions.

In the case of the gold, gold thioglucose, and gold thiomalate subjects, the heavy injections were often associated with a temporary weight drop, followed by slightly increasing weight gains in the subsequent sessions (Figures 2, 7, 9, and 12). The biological effects which had been demonstrated to be associated with the administration of the above compounds are kidney damage and liver damage (i.e., abdominal

organ damage) (Block, Buchanan, and Freyberg, 1942), as well as ventro-medial hypothalamic lesions for gold thioglucose (Wagner and DeGroot, 1963).

In connection with weight changes, the above weight fluctuations noted correspond to Cox, Kakolewski, and Valenstein's (1969) control group weight, rather than the experimental group which had been stereotaxically lesioned in the ventro-medial hypothalamus. The apparently insignificant long-term weight changes in the case of the gold thioglucose-injected subjects at Utah State University argues for an hypothesis that abdominal damage associated with anorexia and hypophagia counters or compounds the characteristic hyperphagia and obesity which accompanies ventro-medial hypothalamic damage; and such damage is assumed to have occurred in all or most of the Utah State University subjects injected with 0.5 mg per gram of body weight or more of gold thioglucose (Wagner and DeGroot, 1963).

Because of the likelihood of extensive damage at both the abdominal as well as the hypothalamic levels, hyperphagia and obesity would probably not be observed due to antagonistic cancelling effects, although other behavioral effects associated with extensive hypothalamic lesions could be expected.

OBSERVATIONS ON THE EFFECTS OF GOLD CHLORIDE

Gold chloride has long been known to be a toxic drug (Drill, 1954), and is consequently no longer utilized in medical practice. The interest in the drug from a behavioral pharmacological point of view stems from the fact that the gold moiety of the compound is highly ionic, providing it with the potentiality of rapidly destroying tissue. Studies of a pharmacological nature concerning its action have consequently not been carried out in decades. Its hypothesized high toxicity had led to the ignoring of the possibility of CNS involvements. Being of no potential importance in medicine or behavioral research, the drug effect was not studied with the more precise operant procedures. It was felt that gross observations would suffice.

Method

Subjects

Two female rats, one of the Long-Evans strain and the other Albino, served as the subjects. The subjects were experimentally naive and were three months of age.

Equipment

Aqueous gold chloride and syringes were available in the laboratory for injection.

Procedures

Because of the attributed toxicity of the drug, the following two

dosages were administered: 20 mg on the first session; skip several days, 50 mg on the second session.

Results

In the case of the Albino rat, following the injection of a 20-mg gold chloride dose no noticeable effects were noted. In 48 hours, a second dose of 50 mg was administered. S was dead in its cage on the following morning. Autopsy performed by the investigator revealed that no clumping or other signs of gold could be found at the site of injection (intraperitoneally).

The Long-Evans subject was also injected with a 20-mg injection of gold chloride initially. Effects were extremely profound, incapacitating the subject so that it was unable to walk by the second post-injection date. Death followed soon afterwards, and consequently a higher dosage was not required.

Discussion of results

Gold chloride is evidently the most toxic of the gold compounds which have been considered. It appears to be completely absorbed within the GI tract, as none was evident intraperitoneally. From the incapicitation of the Long-Evans subject prior to death, massive biological damage could be assumed, although CNS tissue damage could not be ruled out from the evidence noted.

DISCUSSION

R12 received gold, gold thiomalate, and gold thioglucose injections in Experiment 1, providing a meaningful intrasubject comparison, since all effects occurred in the same animal, with its own unique behavioral characteristics.

That the colloidal gold suppressed response rate of the subject was inferred from the rapid increase in response rate that surpassed and doubled that of the original baseline level following discontinuance of colloidal gold administration.

In the experiments which were performed, gold thiomalate was associated with response rate decrement and pronounced downward trends in recorded weights of treated subjects.

Following graduated gold thioglucose administrations, tolerance was evidenced from the relatively stable daily response rates, even with increasing dosages and the relatively minor weight changes observed in the subjects.

In all four gold thiomalate subjects, for example, a correspondence between toxic effects--assumed from loss of weight--and response rate drop was noted. This relationship was particularly evident in R4's record.

In Experiment 3 (i.e., R9, R7, R6, and R11), gold thioglucose was the drug injected. Weight changes were minor, probably due to the lesser toxicity of the compound.

Tolerance of heavier gold thioglucose dosages was noted in R9's chart, where the 25 through 50-mg injections did not affect the

baseline activity during a number of sessions to any appreciable degree.

The second experiment, utilizing R4, R5, and R10, demonstrated the effects of baseline rate for short and long fixed ratios (i.e., FR12 and FR20) with associated gold thiomalate injections. Behavior was rapidly disrupted by higher dosages (i.e., 10 mg to 25 mg, in the case of gold thiomalate), and recovery was very slow on strained fixed ratios. Relearning might definitely be a factor in recovery from gold thioglucose and gold thiomalate effects in view of the many sessions required for recovery of such baselines.

A final 50-mg dose of gold thioglucose proved to be fatal to R7, indicating that the rat could not tolerate large doses of the drug. The data suggest the possibility that injection spacing might affect the maintenance of a tolerance state. An interval spacing of greater than three to four days (e.g., 12 days in the case of R7) might no longer sustain the same tolerance levels in the subject upon subsequent injections.

R6 and R11, responding to low ratios (i.e., FR12) and intermediate response rates (i.e., 25-35 responses per minute), were not demonstrably affected by gold thioglucose (i.e., either steady increase or decrease in response rate). The data point to the importance of the schedule ratio and learned response rate for maintaining baseline behavior. The explanation would probably be that when behavioral response requirements are minimal, or nearly so, the animal can continue responding at a similar rate in spite of toxic drug effects.

An observation that was made in the case of R11's record was that in spite of injections of gold thioglucose up to a final dosage level

of 300 mg (double that required for demonstrable hypothalamic lesions (Wagner and DeGroot, 1963)), no significant daily response rate changes were noted on the graph. This demonstrates that response rates on short ratios may be maintained following the administration of the highest gold thioglucose dose of 300 mg.

Ethological studies on R1 were preceded and followed by escape schedule sessions. The subject was not run the week following the massive gold thioglucose injection to allow for recovery from the initial toxic effects. When R1 was subsequently run on escape, the long periods of non-responding which were observed early in training were no longer evident, although no adequate explanation could be given.

In all studies with gold thioglucose (Wagner and DeGroot, 1963; Mayer, 1960; Debons et al., 1962) that utilized several species, the hypothalamic damage which occurred could be assumed to be of comparable magnitude to that following stereotaxic lesioning of the hypothalamus. Since following stereotaxic lesions, anaphylactic shock has been demonstrated to be reduced in intensity or eliminated (Luparello, Stein, and Park, 1964), the same possibility for chemically-induced lesions was assumed in this investigation. The supporting evidence from a single observation made on the one control and one experimental subject was positive. Since anaphylactic reactions of a minor sort are difficult to differentiate, additional studies and replications would be advisable.

The balance beam apparatus generally indicates that in establishing a behavioral baseline, only a few of the initial responses emitted by the rat subjects were retained. Injections of gold compounds lead to

the reduction of difficult motor responses; particularly, mounting of the beam enclosure--a frequently-emitted response in establishing the baseline prior to the drug injections. The possibility of utilizing the beam apparatus profitably with stimulating drugs was entertained, since with stimulating drugs an expansion of baseline activities could be hypothesized.

Gold chloride was considered worthwhile to study, although it was known to be highly toxic (Drill, 1954) from studies conducted several decades ago. The justification for replication of its effects is that it is a gold compound, its gold being highly ionic (Orestano, 1932), which is the assumed characteristic responsible for its toxicity.

A single gold chloride injection of 20 mg killed R2 within two days, while two injections (25 mg and 50 mg) killed the Albino subject, lending support to the hypothesis that ionic reactivity is associated with toxic effects of gold. The lesser ionic characteristic of the coordination complex compounds, gold thioglucose and gold thiomalate, could well account for their effects, including brain reactivity (i.e., combining with neurological tissue). The greater ionic characteristic of the gold thiomalate compared with that of gold thioglucose (Drill, 1954) would probably account for its greater toxicity when these two similar chelating compounds are compared.

The answer to the problem stated earlier could probably be that gold compounds would have the same effects in humans as they have in the mouse if comparable doses were administered. This is based on the fact that gold penetration of brain tissue has been noted in several species. Such a procedure is inconceivable in humans because of its damage potential. These comparable dosages could be achieved in man

through the development of tolerance induced by gradual dosage increases as demonstrated in this study.

With the gold thioglucose injections administered routinely to humans, lesions are unlikely, although gold deposition in the brain could probably be demonstrated from a spectroscopic analysis.

As for the hypotheses described below based on the experimental data, most were confirmed.

Hypothesis 1: Colloidal gold suppressed behavior. Gold chloride was toxic to the animal and killed it easily. Gold thioglucose and gold thiomalate neither killed all the animals (as would have been the case with gold chloride), nor were they limited to suppressing behavior (as was the case with gold). Instead, they profoundly influenced rates of responding within a day or two after injection. Behavior was often disrupted for a week or two prior to recovery.

Hypothesis 2: Gold thiomalate as well as gold thioglucose were associated with response rate decrements, particularly on the longer ratios (i.e., FR20). A more pronounced and more reliable drop was associated with the administration of gold thiomalate. Associated weight losses generally followed the gold thiomalate administration.

Although gold thiomalate and gold thioglucose have abdominal distributions similar to colloidal gold (Block, Buchanan, and Freyberg, 1942), their brain distributions probably would account for disruptive effects on behavior, where gold seems to only suppress behavior (conclusion from R12 data).

Hypothesis 3: Gold chloride proved to be highly toxic to rats, probably due to its ionic character, as previously postulated (Orestano, 1932).

Hypothesis 4: Colloidal gold, although chemically inert, did affect the subject's behavior; it also suppressed response rate.

Hypothesis 5: Gold thioglucose--assuming that the subject was hypothalamically lesioned--possibly might have prevented anaphylaxis. No generalized conclusion can be made concerning the anaphylactic reaction on the basis of the limited evidence gathered.

Hypothesis 6: Gold thiomalate was more toxic and disruptive of response rate than gold thioglucose, and loss of weight was much more profound following the injections of gold thiomalate when compared with gold thioglucose. This difference could be attributed to the greater ionic character of the thiomalate compound.

Hypothesis 7: Since the work of Denko and Anderson (1944) had indicated that tolerance and cross-tolerance between gold compounds occur in an organism, it would be expected to be expressed behaviorally. Following the gradual increase of gold thioglucose dosages, tolerance was noted behaviorally in constant rates from session to session in one subject (R9). Animals survived heavy dosages of gold thioglucose and response rates were within baseline limits once biological tolerance had been developed in several rats.

Hypothesis 8: Although large hypothalamic lesions were probably associated with a heavy concentration of gold thioglucose administration, hyperphagia and obesity did not follow, probably due to anorexia and hypophagia associated with liver and kidney damage, confounding or countering the hyperphagia resulting from gold thioglucose-induced hypothalamic lesions.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. Gold (colloidal) suppresses response rates on an operant escape schedule. Termination of drug administration leads to an almost immediate increase of response.

2. Gold thiomalate and gold thioglucose decrease response rates significantly with subjects on escape schedules following a fairly large initial dose (i.e., 25 mg for gold thiomalate and approximately 50 mg for gold thioglucose). The decrease occurred more regularly in the case of gold thiomalate.

3. Gold thiomalate is more toxic than gold thioglucose, being associated with a much greater drop in response rate on an operant schedule following an equivalent dosage to gold thioglucose, as well as a temporary loss of weight in the subject.

4. Graduated dosages lead to tolerance of gold thioglucose in rats, so that a formerly considered lethal dose of 1 mg per gram of body weight can be tolerated by the subject.

5. Replication studies with gold chloride confirmed its highly toxic and lethal effects on rat subjects at relatively low dosages (i.e., 25-50 mg).

Recommendations for Medical Therapy with Gold Compounds

1. Results from these studies indicate that should treatment with gold compounds for rheumatoid arthritis be indicated, gold thioglucose

is favored over gold thiomalate because of the apparent greater inferred toxicity of gold thiomalate indicated by the experimental data.

2. A change of scheduling of dosages from the conventional method of an initial 10 mg at intervals to a total of 750 mg (Remington, 1965) to much lower dosages in order to establish and maintain tolerance with fewer undesirable effects.

3. Since clinical evidence, including EEG studies on humans (Patterson and Dale, 1966), indicate brain effects following the administration of gold thiomalate and gold thioglucose, histological and spectroscopic brain examinations on deceased patients who had been on the drugs is recommended. This would probably lead to the removal of the gold compounds from therapeutic utilization.

Behavioral Recommendations

1. Further anaphylactic reaction studies on the effects of gold thioglucose administration on allergic reactions in animals should be undertaken.

2. Studies on the development of tolerance to gold thioglucose in cats, monkeys, and dogs should be undertaken so that the massive dosages required for producing extensive hypothalamic lesions may be achieved. This would allow for the analysis of brain damage-associated behavioral changes utilizing a chemical lesioning technique.

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APPENDIX

Three-Minute Observations Following Placements of a Subject on the High Beam of the Apparatus

	Subjects											
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
1. Weight prior to placements												
2. Passively falls off high beam												
3. Resists but falls off high beam												
4. Stationary on high beam												
5. Mobile on high beam												
6. Rearing on high beam												
7. High and low beam mobility												
8. High-low-high beam mobility												
9. Floor mobility												
10. Stationary on floor												
11. Floor rearing												
12. Return to beams												
13. Beam/floor ratio high or low												
14. Twisting or rolling on floor (ipsilateral)												
15. Turning head on floor (contralateral)												
16. Flip-flops on floor												
17. Number of boluses												
18. Time on beams following five placements												
19. Jumping on top of large enclosure												

Table 1. Frequency percentages of observed behavior over pre- and post-drug sessions

Number		R1	R4	R5	R6	R7	R9	R10	R11	R12	Combined group percent	
						Weight in grams						
1	B[a]	239	257	231	272	282.8	256	258.9	256.1	292.5		
	A[a]	289	258	232	274	297.9	263	266.0	256.8	302.0		
						Percent						
2	B	0	100	0	0	100	0	0	20	0		
	A	33	100	0	0	100	0	0	12	0		
3	B	0	0	0	0	0	0	0	0	0		
	A	0	0	0	0	0	0	0	0	0		
4	B	81	0	0	0	0	0	0	0	0		
	A	100	0	0	0	0	0	0	0	0		
5	B	92	36	9[b]	0	20	10	0	80	30	31	(#5)
	A	0	0	0	0	0	0	0	67	0	11	
6	B	36	0	0	0	0	0	0	80	0		
	A	0	0	0	0	0	0	0	62	0		
7	B	0	0	0	0	0	0	0	10	0		
	A	0	0	0	0	0	0	0	4	0		
8	B	0	0	0	0	0	0	0	0	10[b]		
	A	0	0	0	0	0	0	0	0	0		
9	B	0	100	100	100	100	100	100	90	100		
	A	0	100	100	93	100	92	100	84	100		
10	B	0	0	0	0	0	0	0	0	0		
	A	0	0	20	0	0	0	0	0	0		
11	B	0	100	100	100	100	100	100	100	100		
	A	0	100	80	93	97	84	100	87	100		
12	B	0	100[b]	36	0	0	30	40	10	60	31	(#12)
	A	0	0	20	0	0	8	0	0[b]	5	4	
13	B	100	0	0	0	0	0	0	80	0		
	A	94	0	0	0	0	0	0	92	0		
14	B	0	0	0	0	0	0	0	0	0		
	A	0	0	0	0	0	0	0	0	0		
15	B	0	0	0	0	0	0	0	10	0		
	A	0	0	0	0	0	0	0	49	0		
16	B	0	0	0	0	0	0	0	0	0		
	A	0	0	0	0	0	0	0	0	0		
17	B	9	0	0	0	0	0	0	0	0		
	A	6	0	0	0	0	0	0	70	0		
						Time on beam						
18	B	180	6	5.3	5.1	6	5.3	5.1	100	6.8	35.5	(#18)
	A	170	13	5.2	5.7	11.9	5.1	9.7	113	17.5	39.1	
						Percent						
19	B	0	100	100	71	40	90	80	100	70	72	(#19)
	A	0	41	60	0	24	36	17	83	11	30	

[a]B = Before drug treatments (baseline); A = After drug treatments.
[b]Frequency = Significance cannot be determined.

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